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CIGARETTE SMOKING AND SCHIZOPHRENIA

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M Phil Thesis

The University of Edinburgh

2007

ACKNOWLEDGEMENTS

The author would like to gratefully acknowledge all the assistance given to him by the helpful and ever-obliging staff at the University of Edinburgh's Division of Psychiatry including Patrick Miller, Dr Andrew McIntosh, Dr Andrew Stanfield, Professor David Owens and Professor Eve Johnstone. My special thanks go to Dr David Semple for his patient and at times omniscient supervision.

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ABSTRACT

Section 1 Introduction

Cigarette smoking is anecdotally seen more often amongst schizophrenic than well subjects. Research has suggested a variety of explanations which are discussed; the role of genetics, psychosocial explanations and smoking as self-medication. The financial, physical health and treatment options of and for nicotine dependence are also examined with reference to schizophrenia.

Section 2 Systematic Review of Cigarette Smoking and Schizophrenia

50 studies were identified with a mean prevalence rate of smoking in schizophrenic populations of 66%. Male schizophrenics had a significantly higher ($p=0.04$) rate of smoking and smoked more heavily ($p=0.01$) than females. Different settings were also examined.

Section 3 Meta-Analysis of Case-Control Studies examining the Prevalence of Smoking in Schizophrenia

11 studies were identified that could be examined in a meta-analysis comparing prevalence rates of smoking. Schizophrenic patients were found to be nearly 3 times more likely to smoke than controls.

Section 4 Investigation into Patterns of Cigarette Smoking in Schizophrenia Using Data from the Edinburgh High-Risk Study (EHRS)

At first interview there was a tendency ($p=0.18$) for high-risk group members with psychotic symptoms to have ever smoked compared to other high-risk and control subjects. Schizophrenic controls had a significantly higher prevalence of ever smoking compared to the high-risk and control groups ($p=0.01$). At the

fourth interview there was a trend for high-risk subjects showed a non-significant difference in the rates of ever smoking compared with the controls ($p=0.16$). Those subjects who developed schizophrenia showed a clear trend ($p=0.07$) towards ever smoking

Sections 5/6 Synthesis and Discussion of Results/Conclusion

Explanations for the findings are presented. Although schizophrenia and cigarette smoking are inextricably linked, further studies are necessary if we are to more fully understand the nature of this association.

Section 7 Bibliography

SECTION 1

INTRODUCTION

SECTION 1.0.1 **FOREWORD**

The research carried out for this M Phil has focussed on the intersection between schizophrenia and cigarette smoking. It is almost a truism now that patients with this illness smoke more cigarettes than both the normal population and those who suffer from other psychiatric disorders. This has always left the question of ‘why so?’.

A variety of explanations have been offered to this question, which will be outlined in the systematic review of the literature the author has done, including institutionalisation, self-medication, neurobiology and genetic factors. In addition to searching the evidence base, information from the unique ‘Edinburgh High-Risk Study’ on schizophrenia has been collated and analysed to see if there are further answers to the question posed above.

The thesis itself is divided into introductory sections on schizophrenia, cigarette smoking and their interactions all with an unashamed neurobiological spin. The author shall then describe the hypotheses that have been tested and what meaningful questions can be arrived at from these.

The middle section of the work is divided into the High risk experimental research followed by a systematic review of the literature on cigarette smoking and schizophrenia with a meta-analysis of the data where this was possible.

Finally there is a discussion of how what has been found may be integrated together and what this may mean for present thoughts regarding schizophrenia and its treatment.

SECTION 1.1.1 **What is Schizophrenia?**

Current concepts regarding the aetiology, symptom constellation and management of schizophrenia have changed radically from when Emil Kraepelin (Kraepelin E., 1919/1971) first delineated it from the manic-depressive psychoses. He described a disease entity with “symptoms of mental and emotional infirmity”. His foundation, inherited from Morel (Morel BA., 1860), Kahlbaum (Kahlbaum K., 1863) and Hecker (Hecker E., 1871) has proved a fruitful starting point for researchers since.

The initial dichotomy he outlined in 1896 enabled Bleuler (Bleuler E., 1911/1950) to chart the first classification of schizophrenia into the four A’s of autism, ambivalence, affective incongruity and association of thought disturbances. In conjunction with the work of Kurt Schneider, notably his recognition of the symptoms of first rank, this set of symptoms has persisted in some form into the present day nosological tools of ICD-10 (World Health Organisation, 1992) and DSM-IVR (American Psychiatric Association., 1994).

This standardisation of the diagnosis of schizophrenia has allowed the academic community to begin work on establishing the aetiology, pathogenesis and, ultimately, the treatment of this debilitating disorder.

Table 1 Symptomatic Criteria for Schizophrenia in ICD-10

The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) – (d) below, or symptoms from at least two of the groups referred to as (e) – (h), should have been present for most of the time <i>during a period of one month or more</i> .
(a) Thought echo, thought insertion or withdrawal and thought broadcasting.
(b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception.
(c) Hallucinatory voices giving a running commentary on the patient's behaviour or discussing the patient among themselves or other types of hallucinatory voices coming from some part of the body.
(d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible.
(e) Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content or by persistent over-valued ideas or when occurring every day for weeks or months on end.
(f) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms.
(g) Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism and stupor.
(h) 'Negative' symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or neuroleptic medication
(i) A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

SECTION 1.2.1 Current Aetiological Theories of Schizophrenia

Since the work of Kraepelin numerous studies have investigated the aetiopathogenesis of schizophrenia. Numerous hypotheses have been put forward from the psychodynamic to the genetic. Two models have superseded these now, namely the dopaminergic and neurodevelopmental hypotheses. The author shall elucidate them briefly below to provide a backdrop for the rest of the work within the thesis. It is these two models which have the most explanatory powers when considering the possible links between smoking and schizophrenia.

SECTION 1.2.2 The Dopaminergic Hypothesis of Schizophrenia

This hypothesis proposes that overactivity of dopamine (DA) systems within the brain is the central component of the pathogenesis of schizophrenia. It is one of the earliest, most enduring and influential of the modern neurochemical theories of mental disorder (Baumeister AA. & Francis JL., 2002). Two lines of research have converged on dopamine, firstly the psychotogenic action of amphetamine and secondly the fact that antipsychotic drugs all share, as their primary effect, dopamine receptor blocking actions which correlate with improvements in psychotic symptoms.

The first line of evidence is that amphetamine and other related psychostimulants, all of which enhance dopaminergic neurotransmission via presynaptic mechanisms in central synapses, can induce a psychosis in normal subjects that is similar to schizophrenia (Griffith JD., Cavanaugh J., Held J., *et al*, 1972) in terms of its clinical presentation, course and response to antipsychotics (Sato M., Numachi Y. & Hamamura T., 1992). Furthermore these drugs can activate psychotic symptoms in patients with schizophrenia at lower doses than are required for normal patients to become unwell (Lieberman JA., Kinon BJ. & Loebel AD., 1990) and after an amphetamine challenge there is a greater release of dopamine in schizophrenic patients than in controls (Laruelle M. & A, 1999).

The second line of evidence shows that the majority of antipsychotic medications which improve symptoms block dopaminergic neurotransmission by binding to DA-D2 receptors with an occupancy level of between 60%-80%, the exceptions being clozapine and quetiapine which bind 'loosely' (that is that they have a comparable occupancy but it is for a shorter duration) (Kapur S., 1998) and aripiprazole which acts as a partial agonist (Lieberman JA., 2004). Other pharmacological evidence that has been established is that alpha-flupenthixol, an effective dopamine antagonistic agent, has significant antipsychotic activity whilst its stereo-isomer, delta-flupenthixol, which does not have receptor blocking properties, is therapeutically impotent (Johnstone EC., Crow TJ., Frith CD., *et al*, 1978).

Direct evidence for dopaminergic dysfunction being the biochemical lesion for schizophrenia has come mainly from post-mortem brain studies. These have reported increased dopamine receptor density in the caudate nucleus, putamen and nucleus accumbens (Owen F., Cross AJ., Crow TJ., *et al*, 1978) as well as increased concentrations of DA in the left amygdala and caudate nuclei (Reynolds GP., 1983) of schizophrenic patients. Interestingly it is these very regions in the mesocorticolimbic system that have also been implicated in leading to nicotine dependence in humans as will be outlined in the section below titled ‘The Reward Hypothesis’.

The above account of the pathogenesis of schizophrenia is not definitive however as there remain a number of problems with the evidence. The changes noted in post-mortem studies could be a consequence of antipsychotic treatment which has been shown to increase DA-D2 receptor binding in animal studies (Kornhuber J., Riederer P., Reynolds GP., *et al*, 1989). The pharmacological evidence is blurred in some cases, for example Clozapine has relatively weak DA-D2 receptor blocking properties (Meltzer HY., 1991) and is, as yet, the only weapon in the armamentarium for ‘treatment-resistant’ schizophrenia (Kane JM., Honigfield G., Singer J., *et al*, 1988).

SECTION 1.2.3 The Neurodevelopmental Hypothesis of Schizophrenia

Schizophrenia has increasingly been recognised as a disorder of the brain (Weinberger DR., 1995). From this the neurodevelopmental hypothesis of schizophrenia has been proposed which suggests that brain damage, which later results in the constellation of symptoms listed above, has occurred early in foetal life (Weinberger DR., 1987). Evidence thus far for these cytoarchitectural changes has been predominantly neuropathological in nature (Akbarian S., Bunney WE., Potkin SG., *et al*, 1993) though clinical studies such as the Edinburgh High-risk Study (EHRS) are changing this.

It has been shown that in the period prior to an individual developing the complete illness they differ from normal controls both phenotypically and behaviourally (Baum K. & Walker EF., 1995; Langsley N., Miller P., Byrne M., *et al*, 2005) yet somehow there is a delay due to a compensatory mechanism of some kind (Weinberger DR., 1995). This delay is postulated to occur as a result of the 'faulty wiring' which is laid down as a result of abnormal neurodevelopment which is only exposed after synaptic reorganisation occurs in late adolescence (Buckley PF., 1998). Further evidence for the hypothesis is garnered from the retrospective accounts of patients and third-parties in describing aberrant phenomenology in the months or years preceding the onset of a diagnosable schizophrenic illness (Chapman J., 1966). This work has been furthered more recently by the EHRS which showed that in those genetically predisposed to schizophrenia but still well (mean time to diagnosis 929 days) they showed prominent affective and perceptual changes prior to moving into the prodromal phase or the illness itself (Owens DGC., Miller P., Lawrie SM., *et al*, 2005).

The theory is not without its problems though as the relative contribution of neurodevelopmental dysfunction to the aetiology of schizophrenia remains undetermined as yet (Buckley PF., 1998). Encouragingly, if the dysfunction is regarded as part of a cascade leading to the endpoint of schizophrenia then neurodevelopmental stigmata, such as minor physical anomalies (MPAs), should be observed at an excess rate across the ill population which is indeed the case (Lane A., Kinsella A., Murphy P., *et al*, 1997).

SECTION 1.3.1 **Nicotinic Receptors, Cognition, Information Processing** **Abnormalities and Schizophrenia**

Schizophrenia has classically been regarded as a disease consisting of the positive and negative symptoms described in the codices of ICD-10 and DSM-IV. It has also become apparent that the course of the disease is marked by certain abnormalities of

cognition, broadly defined as the information-handling aspects of behaviour, including information processing abnormalities (Adler LE., Hoffer LD., Wiser BA., *et al*, 1993), working memory dysfunction (Rezvani AH. & Levin ED., 2001) and poor reaction times (De Amicis LE., Wagstaff DA. & Cromwell RL., 1986). These constructs have often been studied as the major foci of neuropsychiatric disorders due to their broad based effects on higher intellectual functions.

It is these particular cognitive processes that have consistently been marked out, by both clinical and animal studies, as being ‘under the influence’ of nicotine as a core neurotransmitter or neuromodulator (Rezvani AH. & Levin ED., 2001). There is also anecdotal and research evidence showing that those affected with schizophrenia smoke a great deal more than those unaffected (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986) and inhale more deeply to gain more nicotine per cigarette than normal smokers (Olinicy A., Young DA. & Freedman R., 1997). What then is the role of nicotinic-acetylcholinergic receptors (nAChRs) in the pathogenesis of schizophrenia?

Nicotine administration and smoking have been shown to have a role in improving the aforementioned cognitive deficits, including sustained attentional function on a variety of neuropsychological tests of attention and vigilance, in normal subjects (Levin ED., Conners CK., Silva D., *et al*, 1998) and those suffering from neuropsychiatric illnesses. Attentional, memory and information processing improvements with administration of nicotine have been noted in those with Alzheimer’s disease (Sahakian B., Jones G., Levy R., *et al*, 1989) as well as schizophrenia (Levin ED. & Resvani AH., 2002). Thus the higher smoking rates found in the schizophrenic population may reflect intentional or inadvertent self-medication of their symptoms.

These more recent studies have been reviewed in light of the work on behavioural phenotypes as foci for studying schizophrenia by Venables (Venables P., 1964). He proposed that sensory overloading, or ‘flooding’, could be a result of a defect in critical brain mechanisms which regulated the perception of incoming sensory

stimuli. These mechanisms were felt to make up an inhibitory filter which might be at fault in schizophrenia particularly with regards to symptoms of paranoia and delusions as patients focus on details that normal people would ignore thus leading to an altered perception of the environment (Ripoll N., Bronnec M. & Bourin M., 2004).

The three phenotypes which are most often studied, including for tobacco research, are smooth pursuit eye movements using an infrared photoelectrode limbus detection device (Tregellas JR., Tanabe JL., Miller DE., *et al*, 2004) and prepulse inhibition (PPI) of startle responses (Braff DL., Geyer MA., Light GA., *et al*, 2001) which is the phenomenon of, in normal subjects, a diminished startle response to a louder startling sound if it has been preceded, approximately 100ms earlier, by a softer sound (Freedman R., Adler LE., Bickford P., *et al*, 1994). The final phenotype is auditory sensory gating (Adler LE., Hoffer LD., Wiser BA., *et al*, 1993) which is measured using an auditory evoked potential (AEP) with a conditioning/testing paradigm. Electrodes on the scalp record a wave with a 50ms latency (P50) following paired auditory stimuli which are given 500ms apart. The normal response is for the subject to have a reduction in the amplitude of the second of the two-paired click stimuli through the action of an inhibitory pathway activated by the first stimulus however in schizophrenia the response to the two sounds is nearly equal (Leonard S., Adler LE., Benhammou K., *et al*, 2001).

It is these filtering mechanisms which seem to be at fault in schizophrenia and lead to the appearance of hypervigilance and corresponding problems with sustained attention. Patients have reported difficulties with maintaining concentration as they feel their sense of awareness overloaded by sensory stimuli which the non-schizophrenic person will automatically screen out as irrelevant background information (Freedman R., Adams CE. & Leonard S., 2000). To illustrate this Freedman et al use the example of a 'patient [who] came to the hospital, terrified the CIA was pounding on her front door every day in an attempt to attack her. A home visit revealed that the pounding noise came from a wrecking crane demolishing some adjacent buildings.' (Freedman R., Adler LE., Bickford P., *et al*, 1994).

Evidence for the nAChRs' involvement in the aetiology and pathogenesis of schizophrenia is also found in neurobiological models that implicate them in the control of response to sensory stimuli due to their activating function on hippocampic interneurons (Freedman R., Adler LE., Bickford P., *et al*, 1994). Using radio-labelled alpha-bungarotoxin it was shown that in seven out of eight schizophrenic subjects studied there was decreased labelling on these cells compared to the brains of matched subjects (Freedman R., Adler LE., Bickford P., *et al*, 1994). This paper also hypothesises that this is a result of one or a combination of three possible faulty neurodevelopmental processes. These are namely failure to migrate, death by apoptosis or neurones lying dormant or inadequately activated by afferent pathways (which cigarette smoking may provide agonism to). Alternatively hippocampal interneuron dysfunction may be the final common pathway for several types of pathophysiology associated with psychosis (Freedman R., Adler LE., Bickford P., *et al*, 1994).

The above work also provides a possible explanation for the finding that these neuropsychological deficit endophenotypes are found in many unaffected relatives of schizophrenic probands (Blackwood DH., St Clair DM., Muir WJ., *et al*, 1991; Siegel C., Waldo M., Mizner G., *et al*, 1984). Gating deficits have been demonstrated in more than 80% of probands but are also present in 50% of their first-degree relatives and at a much lower rate than in the general population (Waldo MC., Carey G., Myles-Worsley M., *et al*, 1991). This loss of inhibition has been shown to be inherited in an autosomal dominant fashion (Freedman R., Adams CE. & Leonard S., 2000). Genetic linkage analysis, using a genome-wide screen, has found that there is significant linkage only at the chromosome 15q13-14 (Freedman R., Coon H., Myles-Worsley M., *et al*, 1997) region which also corresponds with the locus for the alpha7-nicotinic receptor gene. As an addendum to this work, it has been suggested that those relatives with a P50 deficit who do not develop schizophrenia have compensatorily larger hippocampal volumes (Freedman R., Adler LE., Bickford P., *et al*, 1994). It may be that to develop the illness a person has to have a failure of the inhibitory gating mechanism with consequent sensory 'flooding' which results in psychosis only if they have diminished data-processing capabilities reflected in the

smaller hippocampal volumes found in schizophrenic patients (Weiss AP., DeWitt I., Goff D., *et al*, 2005).

Interestingly successful clozapine treatment has been shown to normalise P50 gating dysfunction in schizophrenic patients. This is not the case with typical antipsychotic drugs which have no effect on this (Freedman R., Adler LE., Bickford P., *et al*, 1994). It may be that, because there are relatively few dopaminergic fibres within the hippocampus, the typical DA-D2 receptor blockers have little direct effect on hippocampal function but may partially help information-processing difficulties upstream (without normalising P50 gating). It is unknown, as yet, whether this accounts for the relative differences in efficacy between clozapine and these other medications.

It is important to note that the above story is not restricted to schizophrenia since the electrophysiological and genetic findings are similar with respect to bipolar affective disorder (Freedman R., Adler LE., Bickford P., *et al*, 1994; Turecki G., Grof P., Grof E., *et al*, 2000). It may be that sensory gating deficits are a common aetiological factor in these conditions (McIntosh AM., Forrester A., Lawrie SM., *et al*, 2001).

As well as an integral role in cognition, nicotinic receptors can modulate the rhythmic activity of the hippocampus and other cerebral regions. In addition they can activate a transcriptional factor, CREB, which is felt to be important for developing synaptic plasticity and neuronal development (Dani JA., 2001) as well as providing a possible neuroprotective effect in neurodegenerative diseases including Alzheimer's and Parkinson's diseases (Newhouse PA., Potter A. & Levin Ed., 1997).

SECTION 1.4.1 **Cigarettes – What Are They and What Do They Do?**

SECTION 1.4.2 **The Rise and Rise of the Cigarette**

The first known ethnic group to use tobacco were the Native Americans who were found smoking it by the Europeans who arrived in America. These early settlers in the New World learned to smoke and brought the practice back to Europe with them where it became increasingly popular up to its present day levels of consumption.

The Native Americans generally did not use tobacco recreationally as at extremely high doses tobacco becomes hallucinogenic and therefore it was used as an entheogen. Usually this practice of use was performed only by experienced shamans or medicine men. In addition to being smoked, the uncured tobacco was often eaten, drunk as tobacco juice or even used in the form of an enema preparation. Early missionaries exploring the continent often reported on the state caused by tobacco but as it spread more widely it was no longer used in such large quantities or for spiritual purposes but became a recreational drug of sorts. Despite this global change in the pattern of its use the religious consumption of tobacco is still common among many indigenous peoples, particularly those in South America.

From the beginnings of colonial America, long before the creation of the United States, tobacco played a major part in fuelling the colonization of what was to become the American South. The idea that ‘America was built on tobacco’ is reasonably accurate as the initial colonial expansion was driven by a desire to increase tobacco production which was, at the time, a major source of revenue for the European powers. Ultimately the tobacco crop caused the first colonial conflicts with Native Americans and also led to the use of African slaves for cheap labour in the fields of places such as Virginia from 1619 until their freeing at the end of the American Civil War.

In 1609 John Rolfe arrived at the Jamestown Settlement in Virginia where he was the first man to successfully raise tobacco. The tobacco grown there prior to his arrival, *Nicotiana Rustica*, was not to the liking of the European market but luckily for Rolfe he had brought some seed for the *Nicotiana Tabacum* species with him from Bermuda. Although most of the settlers would not touch his tobacco crop, Rolfe was able to make his fortune farming it.

Shortly before his arrival to Virginia his first wife died and he remarried the legendary Pocahontas, a daughter of Chief Powhatan. When he left for England with her he was now wealthy but unfortunately she died so he returned to his farm and slowly improved the quality of the tobacco. Eventually by 1620, approximately 18000 kilograms of tobacco had been shipped to England and by his death in 1622 Jamestown was thriving as a production capital of tobacco.

The importation of tobacco into Europe was not without resistance and controversy even in the 17th century. King James I of England published the famous polemic titled *A Counterblaste to Tobacco* in 1604. In this essay the king denounced tobacco use as "[a] custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs, and in the blacke stinking fume thereof, neerer resembling the horrible Stigian smoke of the pit that is bottomelesse." In that same year, an English statute was enacted that placed a heavy protective tariff on every pound of tobacco brought into England.

Throughout the 17th and 18th centuries, tobacco continued to be the leading cash crop of the Virginia Colony. Large warehouses filled the areas near the wharfs of new thriving towns such as Richmond and Manchester at the fall line on the James River and Petersburg on the Appomattox River. Until 1883, tobacco excise tax accounted for one third of internal revenue collected by the United States government (Wikipedia, 2005b).

Cigarettes themselves became increasingly popular in Europe during the Crimean War when British troops saw their Ottoman Turkish comrades smoking tobacco

rolled up in newsprint. From there the practice has become increasingly widespread throughout the world (Wikipedia, 2005a).

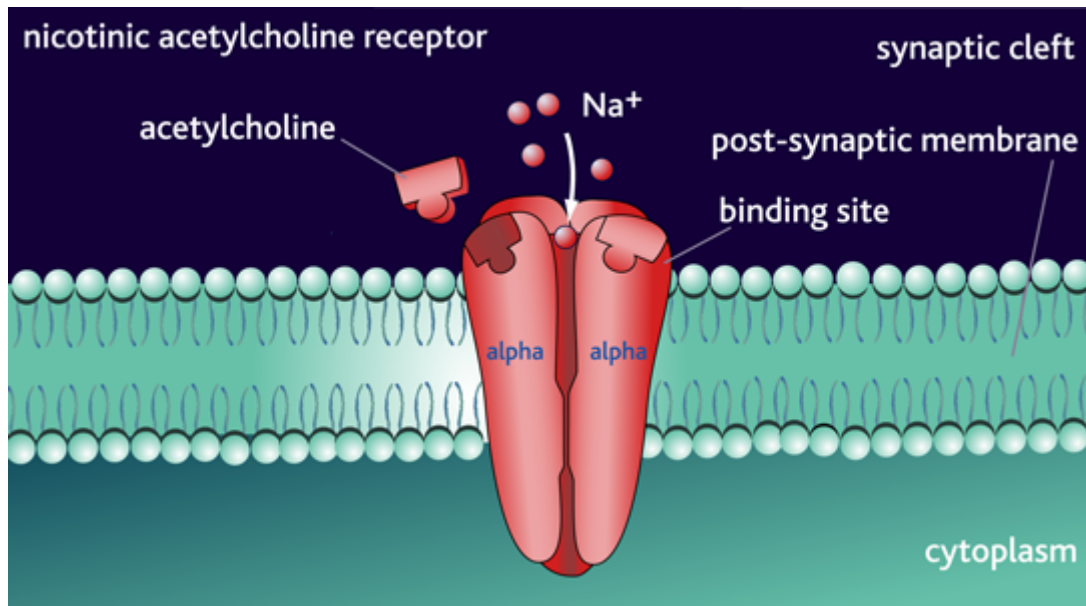
The World Health Organisation estimates 5700 billion cigarettes are now smoked annually every year globally (World Health Organisation., 2004) with 1 million deaths per year reported as being a direct effect of tobacco within the European Union alone (Peto R., Lopez AD., Boreham J., *et al*, 1996).

SECTION 1.4.3 What Do Cigarettes Actually Do to Smokers' Brains?

Nicotine is a tertiary amine composed of a pyridine and pyrrolidine ring which may exist in either D- or L- stereoisomeric forms. Tobacco contains L-nicotine which is the most pharmacologically active form (Dursun SM. & Kuchter S., 1999) and is felt to be the primary psychotropic compound delivered by the cigarette despite its smoke containing 4800 different compounds (Hoffmann D., Hoffmann I. & El-Bayoumy K., 2001). Therefore for the purposes of this thesis it will be regarded that the effects of cigarette smoking within the central nervous system (CNS) are as a result of nicotine mediated by high-affinity nicotinic-cholinergic receptors.

The psychoactive and peripheral effects of nicotine are largely attributable to its molecular similarity to acetylcholine (Watkins S., Koob GF. & Markou A., 2000) with consequent impact on this system. CNS nicotinic-cholinergic receptors are a family of ligand-gated cation channels which are known to be heterogenous due to differences within their subunit compositions (Weiland S., Betrand D. & Leonard S., 2000). . Interestingly, the nicotinic receptor itself was the first neurotransmitter receptor to be identified as a molecular entity and reconstituted in artificial membrane systems still with its physiological and pharmacological abilities intact.

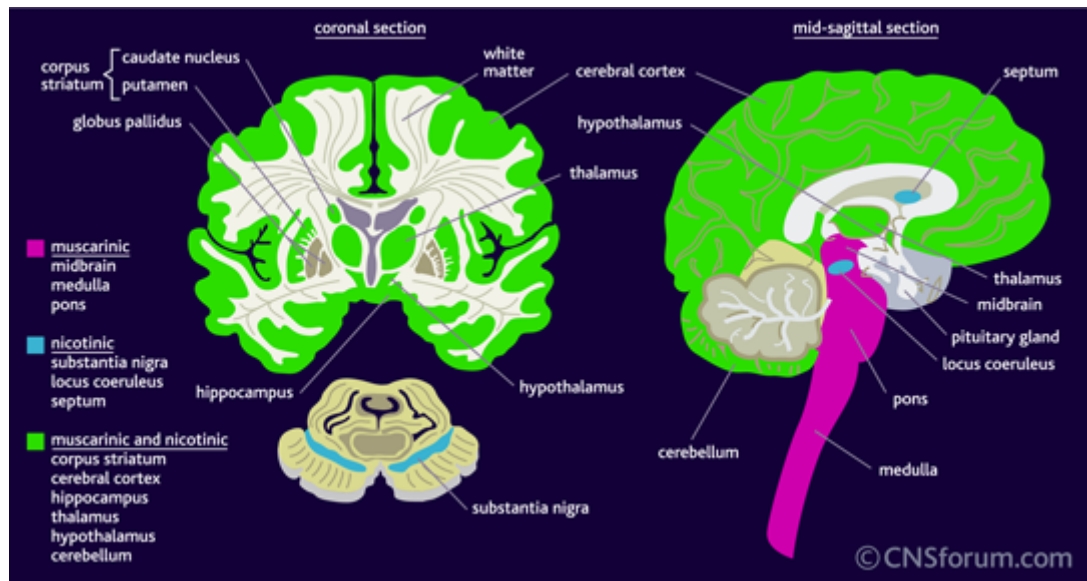
Figure A – Diagram illustrating the nicotinic acetylcholine receptor (www.cnsforum.com, 2005b)



The nAChRs are distributed throughout the brain with the main pathways being the cortical projections from the nucleus basalis magnocellularis and diagonal band (Dursun SM. & Kuchter S., 1999)(see figure B below). They have been implicated in two roles of signal transduction namely in fast synaptic transmission and presynaptic transmitter release modulation (Weiland S., Betrand D. & Leonard S., 2000). The latter affecting a variety of neurotransmitters including acetylcholine, dopamine, serotonin and noradrenaline (Dursun SM. & Kuchter S., 1999) which shall be elucidated in turn.

Nicotine has marked cholinergic effects including causing reduced acetylcholine activity with consequent decreased cortical activity (Armitage AK., Hall GH. & Morrison CF., 1968) and subsequent cortical arousal after nicotine exposure mediated by acetylcholine release. (Dursun SM. & Kuchter S., 1999).

Figure B – The distribution of cholinergic receptors through the brain (www.cnsforum.com, 2005a)

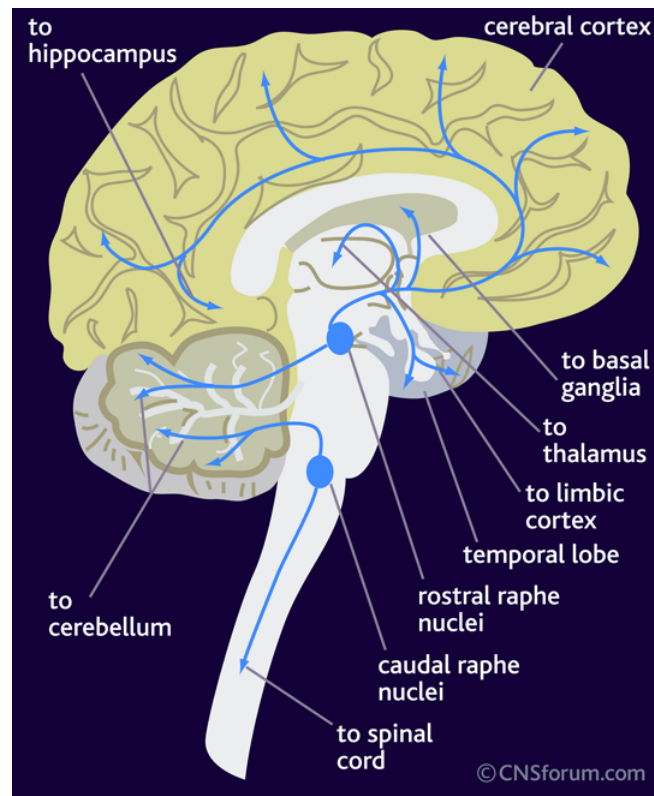


Nicotine's actions through the dopaminergic mesolimbic pathways have been implicated in the behavioural reinforcing effects of nicotine (Corrigall WA., Franklin KBJ. & Coen KM., 1992). Rat studies have shown that ingesting doses of nicotine, which are equivalent to smoking cigarettes, initially activate neurones in these pathways and then produce desensitisation and up-regulation of nicotinic receptors after prolonged exposure (Pidoplichko VI., DeBias M., Williams JT., *et al*, 1997). This may account for tolerance to the psychopharmacological effects of nicotine in people over time as well as being of relevance to nicotine-craving behaviour (Fagerstrom K., 2002).

The raphe nuclei of the lower brain stem contain the majority of serotonin neuron cell-bodies. Their projections emanate from the rostral portion and provide for diffuse innervation of the cortex (see figure C). Nicotine's effects on this system are complex. Animal models have shown that acutely nicotine enhances serotonin release but with chronic administration there is a decrease in serotonin concentration and synthesis within the hippocampus (Foulds J., 1999). Post-mortem studies in humans support the idea of an interaction between nicotine and serotonin receptor subtypes. Chronic smokers have a decreased concentration of brain serotonin and 5HIAA as well as reduced binding of the 5HT-1A agonist 8-OH-DPAT in the hippocampus (Benwell MEM., Balfour DJK. & Anderson JM., 1990). From this it

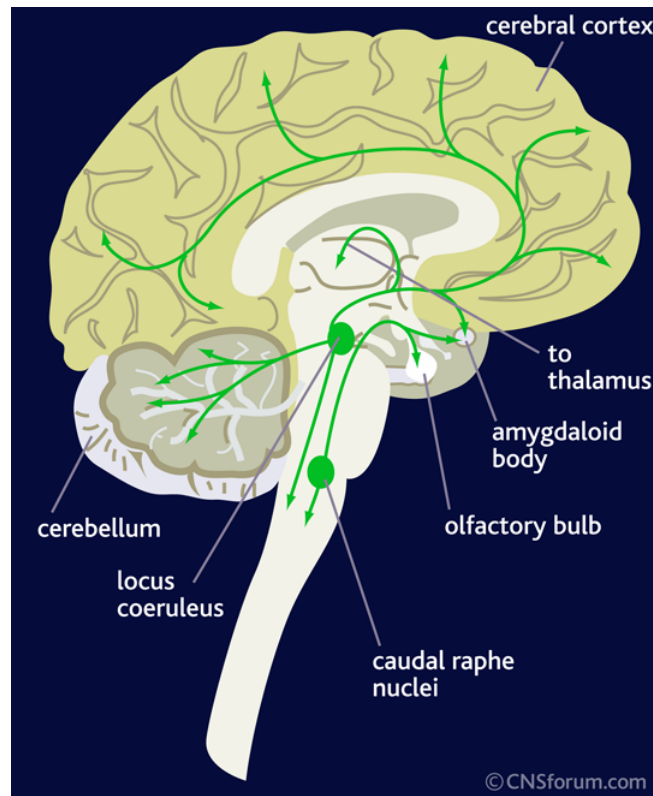
would seem that there is a reciprocal interaction more generally between the nicotinic and serotonergic systems.

Figure C - The serotonergic pathways in the brain (www.cnsforum.com, 2005d)



The noradrenergic system is constructed within the CNS by ascending fibres, in the medial forebrain bundle (MFB), from the locus coeruleus. These innervate the ventral horns of the spinal cord, the cerebellar and cerebral cortices. Hypothalamic and preoptic noradrenergic networks stem from axons which also traverse in the MFB but arise from cell groups of the medulla and pons (see figure D). Nicotine administration, even at low doses, has been shown to increase the firing rate of locus coeruleus noradrenergic neurons (Svensson T. & Enberg G., 1980). This, as well as evidence that chronic administration of nicotine leads to a reduction in frontal cortex noradrenergic activity (Kirch DG., Gerhardt GA., Shelton RC., *et al*, 1987), lends credence to the hypothesis that acute nicotine administration is associated with noradrenergic turnover increases and chronic infusions cause reduced noradrenaline turnover by desensitisation (Balfour DJK., 1989).

Figure D - The noradrenergic pathways of the brain (www.cnsforum.com, 2005c)



The majority of the studies described above have been reliant on animal experiments to identify the effects on the brain of nicotine or smoking. Advances in techniques over recent years, particularly functional magnetic resonance imaging, have demonstrated that nicotine affects the same brain regions in humans as it does in animals. The first such study, albeit limited by its high dosages of nicotine which were given intravenously rather than by smoking, showed dose-dependent increases in neuronal activity. These changes were found in brain regions including the nucleus accumbens, amygdala and frontal lobes (Stein EA., Pankiewicz J., Harsch HH., *et al*, 1998). This work has been furthered showing a biphasic relationship between reticular activation and nicotine dose which in the right hemisphere correlated with nicotine-cravings. It also demonstrated that nicotine increased regional cerebral blood flow (rCBF) in the left frontal region and decreased rCBF in the left amygdala (Rose JE., Behm FM., Westman EC., *et al*, 2003).

As well as these functional imaging studies there has also been recent work published which examined post-mortem brain tissue from the hippocampi of

schizophrenic smokers and non-smokers in comparison with smoking and non-smoking well controls (Mexal S., Frank M., Berger R., *et al*, 2005). More specifically the investigators in this study were attempting to identify functionally related genes that were differentially expressed between smokers and non-smokers in addition to the effects of psychopathology on these results. In all 277 genes were expressed differently in smokers compared with non-smokers regardless of mental health status of which significant over-representation was found in areas of cell motility, immune responses genes and NMDA post-synaptic density (NMDA-PSD). The latter was felt by the authors to support the hypothesis of a close interaction between nicotinic and glutamatergic function which was in turn suggestive of a marked change in excitatory neurotransmission in smokers' brains.

Such a change in neurotransmission might have beneficial effects on sensory processing (Leonard S., 2003) or cognition (Levin ED. & Simon BB., 1998). One of the former study's authors, Sherry Leonard, has suggested that "one reasons persons with schizophrenia smoke is that they are self-regulating. Gene expression seems to be normalized by smoking [in these individuals]" (Kuehn BM., 2006). The self-medication hypothesis is one I will elucidate in further detail later in the thesis.

From the above it is clear that cigarettes, as nicotine delivery devices, are potent psychotropic instruments particularly in the domains of arousal and reward.

SECTION 1.5.1 **Nicotine Dependence and Why Do People Smoke?**

All tobacco products contain nicotine which is readily absorbed in the lungs, mouth and nose before being rapidly transferred via the pulmonary alveolar circulation to and across the blood-brain barrier within 10-20 seconds of administration (Henningfield JE., Stapleton JM., Benowitz NL., *et al*, 1993). Its propensity to lead to addiction is beyond dispute as can be seen from the huge numbers who continue to smoke (World Health Organisation., 2004) in the face of consistent health warnings.

The awareness of this has led to its use, abuse and dependence being classified in both the ICD-10(World Health Organisation, 1992) and DSM-IV (American Psychiatric Association., 1994) (see table 2 below).

Table 2 Symptomatic Criteria for Nicotine Dependence in ICD-10

(1) A strong desire or sense of compulsion to take the substance
(2) Difficulties in controlling substance taking behaviour in terms of its onset termination or levels of use
(3) Physiological withdrawal state when substance use has ceased or been reduced, evidenced by either of the following: the characteristic withdrawal syndrome for the substance or use of the same (closely related) substance with the intention of relieving or avoiding withdrawal symptoms
(4) Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve the effects originally produced by lower doses
(5) Progressive neglect of alternative pleasures or interests because of psychoactive substance use and increased amount of time necessary to obtain or take the substance or to recover from its effects
(6) Persisting with substance use despite clear evidence of overtly harmful consequences (physical or mental)

As a preamble to some of the explanations that follow in this introductory section it is worth bearing in mind Orford's (Orford J., 1985) comment which warns against adopting a unitary theory of addiction or dependence.

“[Appetitive behaviour] can serve many different functions for different people and in addition it can serve different functions for a single individual”.

Such functions may be biological, psychological, social or a combination of these three in nature. For the purposes of this introduction I will outline the major models of addiction and dependence as they pertain to nicotine generally rather than concentrating on this chemical's interaction with schizophrenia specifically as this will be dealt with fully in the discussion section to allow comparison with the experimental and systematic review results.

SECTION 1.5.2 Genetic Factors and Their Effects on Liability to Nicotine Dependence in the Normal Population

There have been a number of family, adoption and twin studies that have reported a genetic influence on smoking. One family study reported that in subjects aged between 20 and 60 years old those whose parents' smoked during the subject's adolescence were more likely to be smokers (52%) than those (20%) whose parents' did not smoke during the same period (Hughes JR., 1986). This study however was limited by the possible confounding effects of non-genetic factors. More conclusive genetic evidence is found from a recent adoption study which showed there was a moderate to strong association between adoptees' smoking and that of their biological siblings. It also demonstrated a similar link between male adoptees' and their biological mothers' smoking (Osler M., Holst C., Prescott E., *et al*, 2001).

Twin studies, which compare the concordance of behaviours in monozygotic twin pairs with the same behaviours in dizygotic twins, have estimated the heritability of initiation of regular smoking in a range of 37% (Kaprio J., Sarna S., Koskenvuo M., *et al*, 1978) to 84% (Heath AC., Cates RC., Martin NG., *et al*, 1993) in women and 28% (Heath AC., Cates RC., Martin NG., *et al*, 1993) to 84% (Heath AC., Cates RC., Martin NG., *et al*, 1993) in men. In the more powerful research design of studies where twins have been reared apart, one of the most methodologically rigorous studies concluded that 60% of the variance in regular tobacco use amongst men and women born after 1940 was attributable to genetic factors (Kendler KS., Thornton LM. & Pedersen NL., 2000).

The two main possible explanations for how smoking behaviour, as an endophenotype, is determined by the individual's genotype are felt to be variations between personalities and differential responses to nicotine between smokers and non-smokers.

A number of personality traits have been identified which predict future smoking and appear to have a genetic basis, namely extroverted / neurotic traits (Eysenck HJ.

& Eaves EJ., 1980) and antisocial traits (Hughes JR., 1986). Smokers also score higher on Eysenck's psychoticism (reflecting emotional coldness, egocentricity and hostility), extroversion and, in some cases, neuroticism scales even on a prospective basis (Cherry N. & Kiernan K., 1976). This may occur because smoking decreases their higher anxiety (reflected in the elevated neuroticism score) as well as increasing their ability to concentrate on their environment (Hughes JR., 1986). The studies about antisocial personality and smoking are still confounded by whether or not such traits cause smoking or are as a result of a genotype that causes both antisocial traits and substance use.

Recent research has demonstrated differences between individuals in the structure and expression of the DA-DR2 receptor gene on human chromosome 11q23 (Eubanks JH., Djabali M., Selleri L., *et al*, 1992). Such polymorphisms result in alterations of dopamine availability from tobacco smoking which in turn may lead to alterations within the reward system of the brain. Those with an enhanced reward when exposed to the dopaminergic agent, i.e. a cigarette, may end up being more prone to nicotine dependence (Noble EP., 2000)

In a recent review on the genetic influences of smoking behaviour and nicotine dependence it was noted that some of the genes which are considered to be associated with schizophrenia overlap with some of those that are connected with nicotine dependence. These include those that encode for the DA-D2 receptor, as above, which allows for the hypothesis that "smoking among family members with genetic loading for schizophrenia may be a risk factor for [getting] the disease" (Yoshimasu K. & Kiyohara C., 2003) though the author acknowledges the role of environmental factors in the strong relationship between schizophrenia and smoking. This topic and its vital impact on my results will be returned to in the discussion section.

SECTION 1.5.3 The Self-Medication Hypothesis

This theoretical model has been regarded as one of the most intuitively appealing ideas about why people abuse substances (Glass R., 1990). It provides a possible link between an individual's biological or psychological vulnerabilities and their substance of choice's effect on ameliorating these problems (Khantzian EJ., 1997). This model initially was developed from Khantzian's psychodynamic psychotherapeutic approach (Khantzian EJ., 1985) but has increasingly been recognised as being partly related to the negative reinforcement process as users take drugs to avoid specific mood states (Eissenberg T., 2004) and, in the case of schizophrenia, partly related to treatment of its underlying cognitive processing difficulties and other problems associated with the disorder and its treatment (Leonard S., Adler LE., Benhammou K., *et al*, 2001) (McEvoy JP., Feudenreich O., Levin ED., *et al*, 1995).

In the general population a significant association has been shown between nicotine dependence, depression and other measures of subjective distress. One of the studies in this area demonstrated that smoking rates rose and quit rates fell as depressive symptoms increased (Anda RF., Williamson DF., Escobedo LG., *et al*, 1990). Such studies though do still leave the essential question for the self-medication hypothesis as to which direction the line of causality moves in. Does smoking precipitate mental illness and subjective distress; do the latter lead to initiation of the former or have the two occurred together coincidentally? Prospective studies have begun to look at this question, one of which illustrated that increased rates of smoking in normal teenagers correlated with greater levels of emotional distress 2 years previously (Orlando M., Ellickson PL. & Jinnett K., 2001) though this work noted that tobacco itself may cause affective distress. Recent work (Riala K., Hakko H., Isohanni M., *et al*, 2005) looking prospectively at rates of cigarette smoking in a large Finnish birth cohort showed that initiation of regular smoking was significantly more closely related to the onset of schizophrenia as compared to other psychoses. Despite such results authors have, as yet, been unable to conclusively answer (Eissenberg T., 2004) this chicken or egg dilemma but it remains one of the foci of this thesis.

As with measures of subjective distress and their interface with the possible role of cigarette smoking as an attempt at self-medication, the role of nicotine as a cognitive performance enhancer has been extensively investigated in normal and unwell subjects (Glautier S., 2004) (and see section 1.4.3). These studies have been noted to be confounded in some cases by a failure to isolate the contaminating effects of nicotine withdrawal (Glautier S., 2004) which causes attentional impairments (Hatsukami D., Fletcher L., Morgan S., *et al*, 1989). Thus to negate this effect research has been focussed on non-smokers and the effects of transdermal nicotine patches rather than cigarettes, due to the obvious ethical dilemmas posed by making non-smokers smoke. This research has shown that low dose patches (7mg/day) significantly improve performance on the Conners Continuous Performance Task (CPT) in such a group (Levin ED., Conners CK., Silva D., *et al*, 1998). Another study has added to this work demonstrating that alcohol consumption, which disrupts performance on a number of cognition tasks, increases smoking behaviour in normal subjects which may be as a means of compensating, or medicating, for these disruptions (Glautier S., Clements K., White JA., *et al*, 1996).

As has been suggested in section 1.3.1, the deficits in information processing that are present in schizophrenia as well as the affective changes that are recognised as components of the illness (World Health Organisation, 1992) may provide enough impetus in those with it to attempt, despite the concomitant risks involved, to self-medicate by smoking cigarettes.

SECTION 1.5.4 The Reward Hypothesis – The Role of Positive Reinforcement in Maintaining Cigarette Smoking

Reinforcement is said to occur when an animal's behaviour yields an outcome that increases the likelihood of that behaviour in the future. In nicotine's case it can be positive, meaning that the behaviour of cigarette smoking produces a rewarding event that would not have occurred otherwise or negative such that the behaviour

leads to termination or avoidance of an adverse event (Eissenberg T., 2004). I shall discuss the former in this section and the latter in the next.

Nicotine produces many positive rewarding and reinforcing effects on administration to humans including inducing mild euphoria (Pomerleau OF. & Pomerleau CS., 1992), increasing energy, heightening arousal, reducing stress and alleviating anxiety (Jarvik ME. & Schneider NG., 1992). In addition to these positive effects there has been the characterisation of a nicotine abstinence syndrome after chronic nicotine exposure (Hughes JR., Gust SW., Skoog K., *et al*, 1991) which has both somatic and affective components. In the acute phases of withdrawal the somatic elements include bradycardia, gastrointestinal discomfort with increased appetite and often weight gain. The affective symptoms include depressed mood, dysphoria, irritability, anxiety, with elevated reactivity to environmental stimuli and concentration difficulties (American Psychiatric Association., 1994; Hughes JR., Gust SW., Skoog K., *et al*, 1991). Continued abstinence carries with it enduring withdrawal symptoms such as depressed mood (Hughes JR., Gust SW., Skoog K., *et al*, 1991) and strong cravings for tobacco (Hughes JR., Hatsukami DK., Pickens RW., *et al*, 1984).

The acute positive reinforcing effects are vital in establishing self-administration behaviour but how this leads from the first puff of a cigarette to drug dependence is still not clear. It has been hypothesised that it may involve neuroadaptation within neural circuits that leads to positive reinforcement and in turn a negative affective state upon discontinuation of nicotine that acts as a negative reinforcer (Koob GF., 1996).

The mesocorticolimbic dopaminergic system that projects from the ventral tegmental area (VTA) to the nucleus accumbens (NA) and prefrontal cortex (PFC) (Corrigall WA., Franklin KBJ. & Coen KM., 1992) has been found to be an important neurological substrate for the euphoriant and reinforcing effects of addictive drugs (Watkins S., Koob GF. & Markou A., 2000). Animals will self-stimulate these regions with electrical intra-cranial current thus implicating them for having hedonic potential as well as the fact that all drugs of abuse increase dopamine in the NA (Milner PM., 1991). The stimuli that do induce relapse of abstinence such as stress,

drug-associated cues and small priming doses as well as the fact that dopamine agonists induce craving for nicotine in humans are further evidence for this system's role in causing dependence (Chambers RA., Krystal RH. & Self DW., 2001).

More specifically, neurobiological animal studies of nicotine reinforcement using intravenous self-administration of nicotine have shown that nicotine activates nicotinic acetylcholinergic receptors in the mesocorticolimbic system. Other non-dopaminergic systems such as the cholinergic, glutamatergic, gamma-aminobutyric acid (GABA) and opioid peptide systems may influence nicotine reinforcement systems but much of the data to date indicates that all of these ultimately interact with the midbrain dopamine system (Watkins S., Koob GF. & Markou A., 2000).

The dopaminergic system seems to be critical in mediating the acute positive reinforcing effects of nicotine, a hypothesis that is supported by the studies that showed that systemic administration of nicotine produces a dose-dependent increase in extracellular dopamine levels in the NA, a neurochemical effect shared by other positive-reinforcer drugs. Nicotine also seems to cause a greater dopamine release by direct binding on nAChRs within the VTA than by direct infusion into the NA (Nissel M., Nomikos GG. & Svensson TH., 1994). This nAChR activation in the VTA is also followed by desensitization which occurs at different rates suggesting that there are multiple classes of the receptors with different activation-sensitization profiles (Pidoplichko VI., DeBias M., Williams JT., *et al*, 1997). This may be why smokers report the first cigarette of the day as being the most pleasurable (Russell MA., 1989) as their recovered nAChRs in the VTA, when re-activated during the morning, give a greater dopamine release than later on (Watkins S., Koob GF. & Markou A., 2000).

Cholinergic interaction with the mesolimbic dopamine systems may be part of the key which allows nicotine to open the door on dopamine release. In rats (Corrigall WA., Coen KM. & Adamson KL., 1994) administration of mecamylamine, a non-competitive nAChR antagonist, blocks nicotine self-administration which indicates that activation of nAChRs is part of the reinforcing action of nicotine. However the same animal study showed that partial lesions of the pedunculopontine nucleus failed

to block self-administration of nicotine showing that cholinergic input alone may not be needed for the reinforcing actions as exogenously administered nicotine may directly stimulate nAChRs in the VTA which in turn affect dopamine release and transmission.

The role of the glutamatergic system in the positive reinforcing effect of nicotine has been increasingly investigated in recent years particularly the excitatory role that N-methyl-D-aspartate (NMDA) receptors in the VTA have to play in modulating the nicotine-dopamine diathesis (Watkins S., Koob GF. & Markou A., 2000). Nicotine activates nAChRs found on presynaptic glutamatergic terminals causing increased glutamate release (McGehee DS., Heath MJS., Gelber S., *et al*, 1995) which has a knock-on excitatory action at NMDA receptors situated on VTA dopaminergic neurons leading to dopamine release in the NA (Hu XT. & White FJ., 1996).

Support for GABA affecting dopaminergic neurotransmission is found in a number of studies. Most notable is that enhancement of GABAergic neurotransmission through giving gamma-vinyl-GABA (GVG), an irreversible inhibitor of GABA transaminase and hence an indirect GABA agonist, stopped nicotine induced dopamine rises in the NA and hence its positive reinforcing effects (Dewey SL., Brodie JD., Gerasimov M., *et al*, 1999).

The impact of the opioid peptides on the reward hypothesis are less clear cut however nicotine does affect their release as has been shown by raises in opioid peptide tissue levels in the NA post administration of nicotine (Houdi AA., Pierzchala K., Marson L., *et al*, 1991) where it is postulated they occupy high-density mu-opioid receptors (Watkins S., Koob GF. & Markou A., 2000). Beyond this mesolimbic area of positive reinforcement there may be a parallel reward system situated in the hypothalamus (Houdi AA., Pierzchala K., Marson L., *et al*, 1991). nAChRs in this region are stimulated by exogenous administration of nicotine which leads to the release of the pro-opiomelanocortin peptide group which includes the precursor to beta-endorphin. It is this latter chemical which is thought to be rewarding in that it may decrease the stress response and facilitate relaxation (Herz

A., 1997). As a counterpoint to the above, attempts at using naloxone, an opioid receptor antagonist, have proved fruitless on changing smoking behaviours (Nemeth-Coslett R. & Griffiths RR., 1986).

The serotonergic system has been shown to have some interactions with nicotine and nAChRs throughout the CNS, as described in section 1.4.3, which would provide a potential neurological substrate for positive reinforcing effects but there has been limited evidence for this as yet (Watkins S., Koob GF. & Markou A., 2000). More clear is their possible effect when smokers quit which the author shall delineate in the following section.

SECTION 1.5.5 The Reward Hypothesis – The Role of Negative Reinforcement

As stated above nicotine can be regarded as a negative reinforcer (Eissenberg T., 2004) with abstinence from its chronic administration providing a readily observable withdrawal syndrome (Hughes JR., Gust SW., Skoog K., *et al*, 1991) which subjects will perform drug self-administration to reduce or terminate (Levin ED., Westman EC., Stein RM., *et al*, 1994).

One model within this theory is the opponent-process model first articulated by Solomon and Corbit (Solomon RL. & Corbit JD., 1973) which describes internal processes that regulate an organism's affective state and/or reward threshold as running awry after repeated drug administration (Eissenberg T., 2004). Hence when nicotine is taken via a cigarette it is hypothesised that there is a temporary reduction in the reward threshold leading to more neutral events seeming more rewarding (Koob GF. & Le Moal., 1997). However other internal processes, namely changes in neurobiological circuitry (Watkins S., Koob GF. & Markou A., 2000), begin to oppose this drug-induced reduction in reward threshold by working to increase it therefore leading to a more permanent change in the 'hedonic set-point' (Koob GF. & Le Moal., 1997). This increase means that when the drug is discontinued events

that were mildly rewarding seem only neutral and events that were previously only mildly unpleasant become markedly unpleasant resulting in avoidance of the negative affective state of withdrawal by smoking (i.e. negative reinforcement) (Eissenberg T., 2004).

On a molecular level during chronic nicotine exposure nAChRs become desensitized, inactivated and finally upregulate after chronic exposure to nicotine to maintain a baseline level of synaptic activity (Dani JA., 1996). This process may occur on reward or non-reward-related cholinergic pathways so that when the smoker quits the recovery of receptors may contribute to the negative affective and somatic withdrawal states which may be being self-medicated against during addiction (Dani JA., 1996).

Neurochemically there are also adaptations after chronic nicotine exposure to the dopaminergic system with decreased tissue levels of dopamine in the nucleus accumbens found after spontaneous withdrawal (Fung YK., Schmid MJ., Anderson TM., *et al*, 1996). This reduction has been proposed to be due to nicotinic receptor desensitisation leading to decreased neuronal firing which has been noted in the VTA after chronic continuous nicotine infusion (Watkins S., Koob GF. & Markou A., 2000). Alongside this and in accordance with the opponent-process model intracranial self-stimulation reward thresholds are elevated in rats during nicotine withdrawal (Watkins S., Stinus L., Koob GF., *et al*, 2000). This may reflect changes in their dopaminergic systems as they are not receiving enough nicotinic agonist to activate nAChRs in the pedunculopontine nucleus which would activate dopaminergic neurones in the VTA (Watkins S., Koob GF. & Markou A., 2000).

Further clarification of the pharmacological mechanism of withdrawal and it's consequent impact as a negative reinforcer can be found by looking from the other end of the telescope at drugs that have been used to aid smoking cessation.

Bupropion is one such drug which, since its introduction in 1989, has clearly demonstrated efficacy as an “atypical” antidepressant with a good tolerability profile (Feighner JP., Gardner EA., Johnstone JA., *et al*, 1991). It is of the aminoketone

class (Wikipedia, 2006) and as such is chemically unrelated to either the tricyclic antidepressants, monoamine oxidase inhibitors or selective serotonin reuptake inhibitors (Stahl SM., Pradko JF., Haight BR., *et al*, 2004). Bupropion's mechanism of action has been shown in animal studies to be not the serotonergic system but rather it (and its active metabolite hydroxybupropion's) efficacy derives from their ability to dually reduce noradrenergic and dopaminergic reuptake (Feighner JP., Gardner EA., Johnstone JA., *et al*, 1991). Furthermore acute administration of bupropion reduced firing of dopaminergic and noradrenergic neurons in a dose dependent manner (Ascher JA., Cole JO., Colin J-N., *et al*, 1996) which is consonant with the activation of an inhibitory feedback loop that would occur as synaptic levels of dopamine and noradrenaline increase.

It is these latter properties of noradrenergic and particularly dopaminergic reuptake inhibition that are of interest for this thesis as bupropion is licensed not only as an antidepressant but also as an aid to smoking cessation. Its anti-craving and anti-withdrawal effects for cigarettes, the reason for its licensure, are felt to be due to its actions on the dopaminergic system (Stahl SM., Pradko JF., Haight BR., *et al*, 2004). As there is a reduction in dopaminergic tissue levels in the nucleus accumbens during spontaneous smoking cessation (Fung YK., Schmid MJ., Anderson TM., *et al*, 1996) and the administration of bupropion has been shown to increase extracellular levels of dopamine and noradrenaline in this area in rats (Nokikos GC., Damsma G., Wenkstern D., *et al*, 1989) there may be a possible mechanism for reducing the symptoms associated with withdrawal with this drug.

The above is in accord with the idea of the "hedonic set-point" (Koob GF. & Le Moal., 1997), mentioned earlier in section 1.5.5, with bupropion providing a means of 'lowering the hedonic thermostat' to a point whereby cravings and withdrawal effects might be easier to endure as has indeed proved to be the case (Johnston JA., Schmidt G., Ascher JA., *et al*, 2002).

The glutamatergic system is also affected by nicotine withdrawal with increases in the acoustic startle response (Helton DR., Tizzano JP., Monn JA., *et al*, 1997, a

measure which is also increased in schizophrenia and reflects reactivity to environmental stimuli. This evidence was supported by the finding that a pre-synaptic group II metabotropic glutamate receptor agonist completely blocked this response (Helton DR., 1997 #147) presumably as it reversed over-excitation of the glutamatergic system due to chronic nicotine exposure (Watkins S., Koob GF. & Markou A., 2000).

The opioid peptide system also appears to undergo neuroadaptation, most probably receptor downregulation (Watkins S., Koob GF. & Markou A., 2000), during chronic nicotine exposure. Naloxone has also been shown to reduce self-reports of affective and somatic symptoms of nicotine withdrawal in humans (Krishan-Sarin S., Rosen MI. & O'Malley SS., 1999). During nicotine withdrawal there are similarities in rat studies with somatic signs of opiate withdrawal in addition to behavioural changes which are mediated by reduced opioid neurotransmission rather than reduced cholinergic neurotransmission (Watkins S., Stinus L., Koob GF., *et al*, 2000).

In view of the affective changes associated with nicotine withdrawal it is unsurprising to note that there is a component of altered serotonergic neurotransmission in nicotine withdrawal. Chronic nicotine use gives a decrease in the hippocampal concentration of 5HT as well as increasing 5HT-1A receptor numbers in the same area which is purportedly due to a reduction in the activity of serotonergic neurones within the median raphe nucleus (Benwell MEM., Balfour DJK. & Anderson JM., 1990) as reported in section 1.4.3. Hence with this decrease in serotonergic function there may be an increase in depressed mood, impulsivity and irritability which would act as negative reinforcers.

Serotonin's actions may not end there though as 5HT-1A antagonists have been shown to significantly reduce the startle response found in nicotine withdrawal (Rasmussen K., Kallman MJ. & Helton DR., 1997) which may itself be due to the reduction in serotonin's inhibitory action on startle (Watkins S., Koob GF. & Markou A., 2000). Again the connection with schizophrenia and its associated abnormalities of startle response is present.

The final component of nicotine and the effects of its withdrawal on maintaining smoking is found with the idea that corticotrophin-releasing factor may underlie some of the negative affective symptoms reported by smokers. This is based on the observation that during the acute withdrawal period from nicotine there is an increase in circulating corticosterone (Benwell ME. & DJK., 1979).

SECTION 1.5.6 Psycho-Social Explanations for Cigarette Smoking Behaviours

Psychological explanations for why people smoke were, unsurprisingly for the time, influenced heavily by psychoanalytic theory in the middle of the twentieth century. This suggested that smoking was rewarding as it produced pleasant or irritating sensations around the mouth leading to ‘oral erotic gratification’ in individuals who had been ‘orally frustrated’ during childhood perhaps in relation to the weaning process or through inadequacies in the mother-child relationship (Bergler E., 1953). They then might seek symbolic satisfaction as an adult through an oral preoccupation, such as smoking (Jacobs MA., Knapp PH., Anderson LS., *et al*, 1965).

The aforementioned model was then supplanted during the 1960s and 1970s with one that favoured integration into a more bio-psycho-social approach. Social and cultural effects including the influence of family and friends, the cultural stereotype of the smoker and the social rewards of smoking do seem to be important in initiating and allowing the persistence of nicotine dependence (Lohr JB. & Flynn K., 1992).

Socio-economic and environmental factors have also been shown to have implications for who smokes with social class, occupation, work stress and area of residence being chief among these (Lohr JB. & Flynn K., 1992). The greatest prevalence of smoking has been found to be in social class V with the lowest in social class I (Capell PJ., 1978). Smokers also tend to have less education and lower levels of academic achievement while in school (Bewley and Bland 1977 cited in

(Lohr JB. & Flynn K., 1992)). The parallels with what is known about the epidemiology of schizophrenia are unmissable but despite these socio-economic and lifestyle considerations the schizophrenic population still has an extremely high prevalence of smoking (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986).

As has been alluded to in the earlier section on the genetic implications for nicotine dependence there are personality differences between well smokers and non-smokers. Studies have found an association between cigarette use and higher levels of neuroticism, anxiety and psychoticism (Cherry N. & Kiernan K., 1976) as well as risk taking and impulsivity (Williams AF., 1973). It is not unreasonable to think that these trait differences, especially the former three, may predispose people with schizophrenia to smoke.

‘The Psychological Tool Model’ (Myrsten AL., Andersson K., Frankenhauser M., *et al*, 1975) is a further theory that has been proposed which suggests that cigarette smoking behaviour allows the user to manipulate their psychological state under many environmental conditions by the dose-dependent, stimulant-depressant actions of nicotine. Nicotine, as stated above, can cause stimulation of ‘pleasure-centres’, increase alertness and enhance cognitive performance. Other beneficial short-term psychological effects include maintaining levels of performance in the face of monotony and fatigue, elevating attention selectivity and attenuating stress (Eysenck HJ., 1973). Smokers can use cigarettes to both calm and stimulate themselves on different occasions as nicotine is one of the few drugs that can act as a stimulant or a depressant (Schelling TC., 1992). It may be, as is outlined in the discussion, that schizophrenic patients may be using cigarettes in just this way, as self-medication, much as those without the illness report that smoking is pleasurable and helps them feel less anxious, angry, depressed and more alert (Jarvik ME. & Schneider NG., 1992).

As can be seen from the above there are complex interactions between the dopaminergic and other central nervous system neurotransmitters and it is not unreasonable to begin to think that the twin processes of cigarette smoking and

schizophrenia are linked somehow. Particular ideas that will be developed in the discussion will be how the reward hypothesis fits with what is already known about the negative symptoms of schizophrenia, the link between the self-medication model and schizophrenia, how psycho-social factors impact on the interface between smoking and schizophrenia and how the genotype may affect all these subjects.

SECTION 1.6.1 So Why Investigate Schizophrenia and Smoking?

SECTION 1.6.2 Previous Epidemiological Evidence Has Shown an Elevated Prevalence Rate of Smoking in Schizophrenic Patients

Multiple studies have detailed epidemiological data showing that psychiatric patients, including those with a diagnosis of schizophrenia, have elevated rates of being smokers compared with non-psychiatric populations (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986; Leonard S., Adler LE., Benhammou K., *et al*, 2001; Masterson E. & O'Shea B., 1984). The largest and most recent of these studies encompassed 42 other pieces of research in a meta-analysis showing that there is an association between tobacco smoking behaviours and schizophrenia (De Leon J. & Diaz FJ., 2005). The author has aimed to expand on this figure in my systematic review as well as conduct a meta-analysis where possible.

Such research has been carried out across the globe in differing settings but not specifically within a “high-risk” group. The study for this thesis carried out in this type of population may allow for a predictive diagnostic value to be placed on smoking prior to subjects developing the full clinical syndrome of schizophrenia.

Both of these arms, in conjunction with the systematic review, may allow some of the answers to be formulated to the ‘why do schizophrenics smoke more?’ question

as well as conclusively showing the solution to the ‘do schizophrenic patients smoke more?’ enquiry.

SECTION 1.6.3 Acetylcholine May Have a Role in the Pathogenesis of Schizophrenia

As has been outlined in the preceding sections on the role of central nicotinic receptors in cognition, particularly in the domain of information processing, and the possible abnormalities that can occur in this system in schizophrenia, the author felt it would be important to investigate what information there is within the literature to correlate such dysfunction with what is known about the pathogenesis of this illness.

Such an investigation lends itself to considering what strategies may be available to alleviate the putative increase in symptoms that has been suggested to occur with cessation of smoking in schizophrenic patients (Dalack GW., 1996) as well as to evaluate how current treatments interact with the nicotine - schizophrenia diathesis. This latter point is most clearly illustrated with the observation that clozapine, as well as being an effective treatment for schizophrenia, also reduces smoking rates in the unwell (Chatterton R., Sanderson L., Van Leent S., *et al*, 1998; George TP., 1995).

SECTION 1.6.4 Cigarette Smoking has a Financial and Health Impact for Patients

Cigarette smoking is a costly habit to engage in with a total expenditure per individual, assuming a 20 cigarette per day habit in the UK, amounting to £1650 per year (Action on Smoking and Health UK., 2004). A 1995 study in the United States (Lohr JB. & Flynn K., 1992) conservatively (original author’s description) estimated, using early 1990s population data, that approximately 19 720 800 patients with schizophrenia smoked, consuming on average, 1.5 packs per day. This results in

nearly \$20 billion dollars worth of cigarettes smoked by the people who are often least able to afford it.

In addition to the financial implications of smoking there are marked consequences of smoking from a general health perspective also. From Doll's first evidence that smoking increases the risk of developing lung cancer (Doll R. & Hill A., 1950) to his more recent work that demonstrated a rise in vascular, neoplastic and respiratory deaths in smokers (Doll R., Peto R., Boreham J., *et al*, 2004) there can now be no ambivalence about how dangerous a pursuit it is. Research within purely schizophrenic populations has confirmed these findings in the main (Masterson E. & O'Shea B., 1984).

If it transpires that schizophrenic patients are self-medicating or smoking for reasons other than those found in the well population then it behoves the medical profession to establish why and what can be done to furnish them with an alternative, certainly less carcinogenic, treatment.

SECTION 1.6.5 Treatment Options for Schizophrenia and Cessation Programmes for Smoking

In view of the financial and health problems associated with cigarette smoking it would seem that helping schizophrenic patients to stop smoking would be a priority for psychiatrists. This is not confirmed by the literature with only 1 out of 35 (2.39%) patients being advised to stop or reduce their smoking in one Scottish study (Lawrie SM., Buckley LA., Ulyatt BC., *et al*, 1995) and only 12.4% of patients were counselled about smoking by a visiting psychiatrist in the American National Ambulatory Medical Care survey (Himelhoch S. & Daumit G., 2003).

This reluctance to counsel patients regarding their smoking needs to be addressed as patients with persistent major mental illness are, in the wide majority (87%), aware that smoking is detrimental to their physical health (Van Dongen CJ., 1999) and a

substantial proportion, in one study at a level of 40% (Forchuk C., Norman R., Malla A., *et al*, 2002), wish to quit the habit. In one study of those that did wish to stop and who were furnished with a reasonable cessation programme then reasonable abstinence rates were reported with 42% at 7 weeks and 12% at 6 months (Addington J., El-Guebaly N., Campbell W., *et al*, 1998).

The medical implications of smoking are now being increasingly monitored at a society-wide level. The implementation of the smoking ban in public places throughout the UK which will also affect psychiatric hospitals in Scotland early in 2005 (McConnell J., 2004) may have an effect on patients not only in terms of improving their physical health but also in affecting their mental health.

In the light of these policy changes it felt reasonable to examine the prevalence of smoking within the schizophrenic population, establish what can be done to alleviate the problem and begin to examine why it exists in the first place.

SECTION 1.6.6 Anecdotal Evidence

Throughout the 5 years that the author has been working in the field of psychiatry it has been impossible to ignore the consistent ebb and flow of those who suffer from serious mental illness in and out of smoking rooms in hospital. Colleagues and the author have remarked that there must be some explanation for this ranging from those who feel it is an effect of the patients' social milieu to the more biologically inclined explanations that it must relate to their neuropathology. This thesis aims to address some of these explanations and establish if what is seen anecdotally is statistically true.

SECTION 1.7.1 **Hypotheses**

1. Patients with schizophrenia who are inpatients will be more likely to be smokers than their outpatient counterparts.
2. Male patients with schizophrenia will have a higher prevalence rate of smoking compared with female patients.
3. Schizophrenic smokers will have a higher prevalence rate of being heavy smokers than normal smokers.
4. Male schizophrenic smokers will have a higher prevalence rate of being heavy smokers compared to female smokers.
5. Schizophrenic patients are significantly more likely to be smokers than individuals in the well population.
6. The schizophrenic group in the Edinburgh High-Risk Study will have a higher prevalence rate of cigarette smokers compared with the normal population and high-risk groups.
7. Patients at high-risk of developing schizophrenia will have a higher prevalence rate of cigarette smokers compared with the normal control group.

SECTION 1.7.2 **Questions**

1. Are schizophrenics more likely to smoke than other groups and, if yes, why?
2. Are high-risk subjects more likely to smoke than their counterparts who are not at high-risk, and if this is so, why?
3. Does smoking correlate with illness severity?

SECTION 2

A SYSTEMATIC REVIEW OF CIGARETTE SMOKING AND SCHIZOPHRENIA

SECTION 2.1.1 INTRODUCTION

As the initial outline of this thesis was being constructed it became apparent that it would be important to place the results obtained from the Edinburgh High-Risk Study regarding schizophrenia and cigarette smoking in the wider context of what has already been established regarding the association between these two entities.

Therefore the author felt it would be prudent to review the studies that have already been presented regarding the prevalence data of cigarette smoking in schizophrenia as well as extracting any other meaningful portions of data that were available from these. This has allowed for some statistical analyses of differences and similarities within the schizophrenic populations studied. However, in view of the EHRS' focus on what is different about those who are at high-risk of developing schizophrenia compared with those who are not, it also seemed an integral part of this work to analyse studies which have examined cases and controls together. This latter research forms the body of section 3 which is a meta-analysis comparing cigarette smoking rates in schizophrenic and normal populations.

SECTION 2.2.1 METHOD

SECTION 2.2.2 Search Strategy

To enable the greatest cross-section of relevant articles to be available for review a broad search strategy was employed. Electronic searches on online databases was achieved by using the OVID gateway to gain access to -

Journals at Ovid Full Text (as of May 18th 2005)

EBM Reviews – ACP Journal Club (1991 – May 2005)

EBM Reviews – Cochrane Central Register of Controlled Trials (2nd Quarter 2005)

EBM Reviews – Cochrane Databases of Systematic Reviews (2nd Quarter 2005)

EBM Reviews – Databases of Abstracts of Reviews of Effects (2nd Quarter 2005)

EBM Reviews Full Text – Cochrane DSR, ACP Journal Club and DARE

EMBASE (1980 – 2005 Week 20)

Ovid MEDLINE (1966 – May Week 2 2005)

Ovid OLDMEDLINE (1950 – 1965)

PsycINFO (1872 – 1966)

PsycINFO (1967 – May Week 2 2005)

A purposefully wide set of search headings were used due to the variety of ways in which cigarette smoking was seen, from preliminary reading around the topic, to be discussed in the literature. As stated above the primary focus for the review was to isolate epidemiological data on the topic which is shown by the lower half of the search headings below.

SCHIZOPHRENIA

SCHIZOAFFECTIVE

PSYCHOSIS

PSYCHOTIC

TOBACCO

NICOTINE

NICOTINIC

CIGARETTE(S)

SMOKING

SMOKE

RESEARCH	POPULATION
MAJOR CLINICAL STUDY	POPULATION RESEARCH
EPIDEMIOLOGY	CASE-CONTROL
PREVALENCE	EVIDENCE
INCIDENCE	MAJOR CLINICAL STUDY

No language restrictions were applied to the search initially but due to logistical problems (i.e. lack of translation facilities!) I had to exclude most of the studies which were not in English. A number of studies were also unable to be located despite communication with the British Library.

In addition to the electronic search references were hand-searched from this first round of picks and collated a further list of journal articles to be found from these. This process was repeated a further two times. Unfortunately due to time constraints the author was unable to hand-search further journals or communicate with any of the authors of papers' to establish if they had unpublished data which may have been of value to the review.

Where data was reported in more than one article the author extracted the data from either the original study or from the most recent report. If there were uncertainties regarding the data then it was excluded as a whole from the review to ensure non-contamination of the data.

SECTION 2.2.3 Study Eligibility

From the above pool of studies a further selection process was undertaken using the following criteria:

1. Patients must have had a diagnosis of schizophrenia as a pure entity insofar as this was possible to be determined. Clear evidence of mixing of schizophrenic

with schizo-affective, or other psychiatric diagnosis, populations led to exclusion from the review.

2. At least 90% of the participants were aged 16 or over.
3. In the first arm of the review studies were only included if they had data for current rates of smoking amongst the schizophrenic group to enable comparisons to be made and total rates of prevalence to be calculated.
4. In the meta-analysis, case-control studies were included only if they had data for current rates of smoking, again to allow comparisons to be made between groups.

SECTION 2.2.4 Data Extraction

From all studies a variety of variables were extracted where possible:

1. Socio-demographic data including gender, inpatient/outpatient status and country of origin of the study.
2. Current, former, never and ever rates of smoking as totals and by gender where possible.
3. Number of cigarettes smoked with an arbitrary division of this variable into those smoking 1-19 cigarettes per day (CPD) and those smoking 20 or more cpd. Data regarding Fagerstrom Test of Nicotine Dependence (FNTD) results was collected as well as mean CPD smoked though these were not used in the analysis.
4. Schizophrenia subtype data as well as symptomatology scores (e.g. according to the Positive and Negative Syndrome Scale (PANSS) (Kay SR., Fiszbein A. & Opler LA., 1987) where extractable.

5. Age of onset of smoking and schizophrenia where found.
6. Medication doses and type of drug used where found.

Two arms were set up to allow some meaningful analysis of the data to be done. The first of these, found in section 2, looked at prevalence rates of current smoking amongst schizophrenic patients across a variety of settings and countries. The second arm, found in section 3, looked at case-control studies to compare rates of smoking between schizophrenic patients, normal controls and other psychiatric patients. This last group was also separated into one group with a mix of diagnoses and another with purely affective disorders. Unfortunately due to a lack of data these results have not been presented here.

SECTION 2.2.5 Statistical Analysis

Study results from this arm of the study were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. This allowed calculation of prevalence rates of smoking within each study's schizophrenic population as a whole to be compared as well as examining male and female data where available.

Throughout the proceeding analyses the prevalence rate of smoking is the number of current smokers with schizophrenia divided by the total number of schizophrenic patients in the sample. The same method was applied across the genders. Both schizophrenia and current smoking are as defined by the studies themselves.

Data from the tables below were compiled in SPSS thus allowing calculation of descriptive statistics and Mann-Whitney tests where appropriate and applicable. In addition data was then represented within a box and whisker plot form (Figure E) to allow ease of comparison between the prevalence rates of smoking across the three settings.

SECTION 2.3.1 RESULTS

From the total amount of studies identified there were 50 that met the systematic review criteria (Table 3). The main reasons for excluding studies identified from within the original search were as follows;

1. Duplication of studies from original search strategy from internet databases and Reference Manager version 10.0 (RefMan) software.
2. Papers did not deal with smoking cigarettes but instead concentrated on other substances. This was particularly a problem with smoking as it related to cannabis use.
3. Nicotine as a search term picked up a large number of studies focussing on nicotinic acid.
4. Epidemiological data was either not present in the study or was not extractable.
5. Data on schizophrenic patients was not classified separately but was aggregated with schizoaffective disorder or other psychotic disorders more generally.
6. A number of papers were review articles which contained data I had isolated from the original article reported in the review.

SECTION 2.3.2 Analyses of prevalence rates of smoking in schizophrenia across 3 settings

In total 50 studies (table 3) were appropriate for analysis in this section. The table below also illustrates the variability in recording methods for cigarette smoking and for making the diagnosis of schizophrenia. Of these 26 examined patients in outpatient settings, 15 in inpatient settings and 9 in mixed settings.

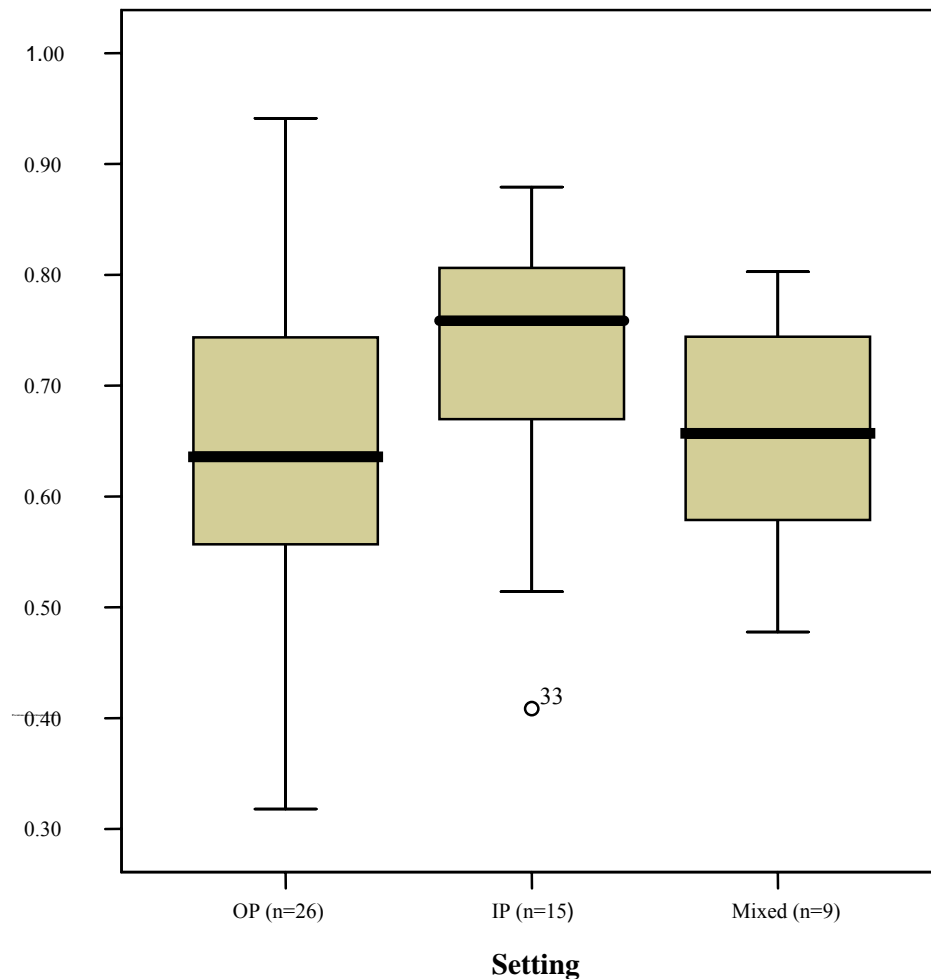
Table 3 Studies with complete data sets for prevalence rates of smoking in schizophrenic populations

Study	Country	How current smoking was determined	How was schizophrenia diagnosed	Setting	Total number in schizophrenic population	Total number of schizophrenic smokers	Prevalence rate of smoking in schizophrenic population
(Altamura AC., 2003)	Italy	Not specified	DSMIII-R	OP	103	74	0.72
(Asaad TAA., 2003)	Egypt	SCID-I	SCID-I (DSMIV)	OP	100	76	0.76
(Bejerot S., 2003)	Sweden	>1cpd for 6mths	No formal Dx	OP	161	79	0.490
(Brown S., 2000)	Scotland	Research record from previous study	Research record from previous study	OP	306	224	0.73
(Brown S., 1999)	Scotland	SCAN	SCAN	OP	102	64	0.63
(Chong SA., 1996)	China	≥5cpd for 6mths	DSMIII-R	OP	195	62	0.32
(Dickerson FB., 2002)	USA	Behavioural risk factor survey	Chart Dx	OP	43	27	0.63
(Diwan A., 1998)	USA	Questionnaire	Own psychiatrist report	OP	63	57	0.90
(El Guebaly N., 1992)	Canada	Addiction Severity Index (ASI)	DSMIII-R	OP	106	65	0.61
(Fowler IL., 1998)	Australia	SCID-R	SCID-R	OP	194	144	0.74
(Goff DC., 1992)	USA	Semistructured interview	SCID	OP	78	58	0.74
(Hamera E., 1995)	USA	Self-report	SCID	OP	17	16	0.94
(Herran A., 2000)	Spain	Fagerstrom Test of Nicotine Dependence (FTND)	SCAN (DSMIV)	OP	64	41	0.64
(Hughes JR., 1986b)	USA	Questionnaire	DSMIII	OP	24	21	0.88
(Itkin O., 2001)	Israel	FTND	DSMIV	OP	64	29	0.45
(Kelly C., 1999)	Scotland	Questionnaire	ICD9	OP	135	78	0.58
(Lyons MJ., 2002)	USA	DSMIII-R	DIS-III-R	OP	24	20	0.83
(McCreadie RG., 2002)	Scotland	Scottish Health Questionnaire	OPCRIT (DSMIV)	OP	250	162	0.65
(McCreadie RG., 2003)	Scotland	Scottish Health Questionnaire	OPCRIT (DSMIV)	OP	102	71	0.70
(Mori T., 2003)	Japan	DSMIV	DSMIV	OP	137	47	0.34
(Srinivasan TN., 2002)	India	Questionnaire	DSMIV	OP	286	109	0.38
(Taiminen TJ., 1998)	Finland	Self-report	Drug trial selection	OP	88	49	0.56
(Uzun O., 2003)	Turkey	DSMIV	SCID (DSMIV)	OP	116	58	0.50
(Vanable PA., 2003)	USA	Questionnaire (Y/N)	SCID (DSMIV)	OP	623	393	0.63
(Chiles JA., 1993)	USA	Pack years smoked	DSMIIIR	OP	80	70	0.87
(Menza MA., 1991)	USA	Questionnaire	DSMIIIR	OP	99	56	0.56

(Carvajal C., 1989)	Chile	Not specified	Not specified	IP	96	78	0.81
(Challis GB., 1999)	Canada	Not specified	Not specified	IP	51	32	0.62
(De Leon J., 1995)	USA	Staff estimate of smoking	DSMIII-R	IP	237	201	0.85
(Llerena A., 2003)	Spain	Not specified	Clinical Dx (DSMIII-R)	IP	100	70	0.70
(Tracy JL., 1996)	USA	Elgin Behavioural Rating Scale (EBRS)	DSMIII-R	IP	400	305	0.76
(De Leon., 2002)	USA	Staff observation / EBRS	Clinical Dx (DSMIII-R)	IP	449	335	0.75
(Liao D-H., 2002)	China	Not specified	DSMIV	IP	257	105	0.41
(McCreadie RG., 2000)	Scotland	Scottish Health Questionnaire	DSMIV	IP	30	22	0.73
(McEvoy JP., 1999)	USA	Not specified	Not specified	IP	22	17	0.77
(Patkar AA., 2002)	USA	FTND	DSMIV	IP	87	66	0.76
(Sandyk R., 1991)	USA	Self report / Staff observation	DSMIII	IP	142	73	0.51
(Sandyk R., 1993)	Italy	Questionnaire / Staff report	DSMIII	IP	111	71	0.64
(Lawrie SM., 1995)	Scotland	Questionnaire	DSMIII-R	IP	15	12	0.80
(O'Farrell TJ., 1983)	USA	Interview with head nurse	Not specified	IP	207	182	0.88
(Masterson E., 1984)	Eire	Questionnaire	Not specified	IP	100	83	0.83
(Beratis S., 2001)	Greece	>100 cigarettes in lifetime and/or smokers who quit <1mth ago	DSMIV	MIX	133 IP 273 OP Total - 406	235	0.58
(Glynn SM., 1990)	USA	Questionnaire	DSMIII-R	MIX	41 IP 18 OP Total - 59	46	0.78
(Kavanagh DJ., 2004)	Australia	DSMIII-R	DIP (DSMIII-R)	MIX	430	320	0.74
(Poirier M-F., 2002)	France	Questionnaire	DSMIII-R	MIX	207	136	0.66
(Calabresi M., 1991)	Italy	Not specified	DSMIII-R	MIX	71	57	0.80
(Akvardar Y., 2004)	Turkey	FTND	SCID	MIX	49	34	0.69
(Ucok A., 2004)	Turkey	Regular cpd >1mth	SCID	MIX	66	38	0.58
(Riala K., 2005)	Finland	Questionnaire	DSMIII-R	MIX	67	32	0.48
(De Luca V., 2004)	Canada	Questionnaire	SCID-IP	MIX	177	108	0.61

As can be seen from the below (figure E, table 4) there is a non-significant difference between the settings in terms of the rate of smoking within their respective schizophrenic populations. This can be seen from the clear overlap of the 95 percent confidence intervals.

Figure E - Box plot of prevalence rates of smoking in schizophrenic populations by study setting



These results show that more people with schizophrenia smoke as inpatients (mean value 72%) than as outpatients (mean value 64%) in this sample though this is not a statistically significant finding. Those studies which contained a mixture of inpatients and outpatients had a mean rate of smoking (66%) which lay between the other 2 groups' values.

The prevalence rate for cigarette smoking when all 3 settings were analysed together was 67% (table 4). The outlier shown (figure E – marked as 33) is the prevalence rate from a Chinese study based in Taiwan (Liao D-H., Yang J-Y., Lee S-M., *et al*, 2002). This value is markedly lower due to the low prevalence of smoking in the female

schizophrenic smokers within the study. The base rate of smoking in the female general population in this region, at 5 percent (Liao D-H., Yang J-Y., Lee S-M., *et al*, 2002), is much lower than in comparison to western countries. As a result even though this study showed an elevated rate of smoking amongst Chinese female schizophrenic patients the overall mean was lowered in relation to the other, predominantly western, studies.

SECTION 2.3.3 Analyses of prevalence rates of smoking in schizophrenia by gender and across settings

From the original set of 50 studies which had data that would allow for calculation of prevalence rates only the 13 listed in table 5 had results that could give a comparison between male and female groups.

Table 5 Studies containing complete data sets for schizophrenic smokers by gender

Study	Setting	Total n	Female n	Male n	Schizophrenic smokers	Male schizophrenic smokers	Female schizophrenic smokers	Prevalence rate of male schizophrenic smokers	Prevalence rate of female schizophrenic smokers
(Bejerot S., 2003)	OP	161	89	72	79	37	42	0.51	0.47
(Brown S., 1999)	OP	102	48	54	64	37	27	0.69	0.56
(Chong SA., 1996)	OP	195	99	96	62	52	10	0.54	0.1
(El Guebaly N., 1992)	OP	106	49	57	65	39	26	0.68	0.53
(Kelly C., 1999)	OP	135	62	73	78	52	26	0.71	0.42
(Mori T., 2003)	OP	137	71	66	47	30	17	0.45	0.24
(De Leon J., 1995)	IP	237	87	150	201	140	61	0.93	0.7
Llerena A., 2003 #274}	IP	100	16	84	70	68	2	0.81	0.13
(De Leon., 2002)	IP	449	114	335	335	236	99	0.7	0.87
(Liao D-H., 2002)	IP	257	130	127	105	90	15	0.71	0.12
(Masterson E., 1984)	IP	100	50	50	83	42	41	0.84	0.82
(Akvardar Y., 2004)	MIX	49	23	26	34	18	16	0.69	0.7
(De Luca V., 2004)	MIX	177	47	130	108	85	23	0.65	0.49

Table 6 Descriptive statistics for prevalence rates of smoking in schizophrenic populations by gender

Setting	Prevalence rate of male schizophrenic smokers Mean (s.d.)	Prevalence rate of female schizophrenic smokers Mean (s.d.)
OP (n=6)	0.6 (0.11)	0.39 (0.18)
IP (n=5)	0.8 (0.10)	0.52 (0.38)
Mixed (n=2)	0.67 (0.27)	0.59 (0.15)
Total (n=13)	0.69 (0.13)	0.47 (0.26)

Again, similarly to table 4, it can be seen that the prevalence rates of smoking in both male and female outpatients' groups (60% and 39% respectively) have a lower rate of smoking than both genders of inpatients (males 80% and females 53%). Studies with a mixed population lay in-between these values for men (67%) but for women there was a higher rate of smoking in this combined setting (59%).

From these results it can be seen that there is a lower prevalence rate for female schizophrenic patients, in this sample, to be smokers compared with their male counterparts across the 3 settings. This is not statistically significant by individual setting however there is greater variation within the female population which may reflect cultural norms in different countries (Liao D-H., Yang J-Y., Lee S-M., *et al*, 2002).

Table 7, below, demonstrates that there is a significant difference ($p=0.04$) between the prevalence rates of smoking amongst schizophrenic populations when they are differentiated by gender. This data is pooled from across the three settings described in table 6.

Table 7 Mann-Whitney U-Test results comparing prevalence rates of smoking in schizophrenic populations by gender

Ranks				
	Sex	Number of studies	Mean Rank	Sum of Ranks
Prevalence rates of smoking within schizophrenic populations	Male	13	16.62	216.00
	Female	13	10.38	135.00
	Total	26		

Test Statistics

	Prevalence rates of smoking within schizophrenic populations by gender
Mann-Whitney U	44.00
Wilcoxon W	135.00
Z	-2.08
Asymp. Sig. (2-tailed)	.04
Exact Sig. [2*(1-tailed Sig.)]	.04(a)

a. Not corrected for ties.

SECTION 2.3.4 Analyses of heavy smoking rates in schizophrenia by gender and across settings

For this analysis heavy smoking is defined as smoking more than 20 cigarettes per day. The prevalence rate was calculated by dividing the number of schizophrenic patients who were 'heavy' smokers by the total number of schizophrenic smokers.

A total of 12 studies had data that would allow the calculations to be performed for the total number of smokers and of these 5 would allow differentiation by gender also (see table 8).

Table 8 Studies containing data for heavy smoking rates (defined as greater than 20 cigarettes per day) as totals and by gender

Study	Setting	Total number of patients with schizophrenia who smoke	Total smokers who smoke more than 20 cpd	Male smokers who smoke more than 20 cpd	Female smokers who smoke more than 20 cpd	Prevalence rates for male smokers who smoke more than 20 cpd	Prevalence rates for female smokers who smoke more than 20 cpd	Prevalence rate regardless of gender of schizophrenics who smoked more than 20 cpd
(Brown S., 1999)	OP	64	53	33	20	0.89	0.74	0.83
(Dickerson FB., 2002)	OP	27	9	0.33
(El Guebaly N., 1992)	OP	65	53	31	22	0.79	0.85	0.82
(Fowler IL., 1998)	OP	144	136	0.94
(Herran A., 2000)	OP	41	18	0.44
(McCreadie RG., 2003)	OP	71	38	0.54
(Srinivasan TN., 2002)	OP	109	26	0.24
(Uzun O., 2003)	OP	58	18	0.31
(Challis GB., 1999)	IP	32	10	0.31
(De Leon J., 2002)	IP	201	90	68	22	0.49	0.36	0.45
(Llerena A., 2003)	IP	70	28	27	1	0.4	0.5	0.4
(Masterson E., 1984)	IP	83	59	34	25	0.81	0.61	0.71

Table 9 Descriptive statistics for prevalence rates of heavy smokers in schizophrenic populations by setting and totals

Setting	Prevalence rate of male schizophrenic smokers who smoke more than 20 cpd Mean (s.d.)	Prevalence rate of female schizophrenic smokers who smoke more than 20 cpd Mean (s.d.)	Prevalence rate of all schizophrenic smokers who smoke more than 20 cpd regardless of gender Mean (s.d.)
OP (n=2)	0.84 (0.69)	0.79 (0.07)	0.56 (0.27)
IP (n=3)	0.56 (0.22)	0.49 (0.12)	0.47 (0.17)
Total (n=13)	0.68 (0.22)	0.61 (0.19)	0.52 (0.24)

Unfortunately due to paucity of data (i.e. 2 outpatient studies with a combined n of 106 and 3 inpatient studies with a combined n of 177) meaningful statistical analyses with this data set was not possible beyond these descriptive remarks. Table 9 shows an opposing result to those in tables 4 and 6 with outpatients of both genders having a higher rate of smoking heavily (84% of male smokers and 79% of female smokers) than male (56%) and female (49%) inpatients. The same applies when the results for the 12 studies with across gender data are analysed with 56% of outpatients smoking more than 20 cigarettes per day compared with 47% of inpatients.

These previous results are in the main not statistically significant as can be seen by the standard deviation values in table 9. It still remains worth highlighting the marked difference between the larger prevalence of female heavy smokers in outpatient settings as compared with the smaller rate in inpatient settings.

Table 10 Mann-Whitney U-Test comparing the prevalence rates of heavy smoking (i.e. >20cpd) by gender regardless of setting of study

Ranks				
	sex	Number of studies	Mean Rank	Sum of Ranks
Prevalence rate of smoking more than 20 cpd	male	5	8.00	40.00
	female	5	3.00	15.00
	Total	10		

Test Statistics

	Prevalence rates of heavy smoking
Mann-Whitney U	.00
Wilcoxon W	15.00
Z	-2.62
Asymp. Sig. (2-tailed)	.01
Exact Sig. [2*(1-tailed Sig.)]	.01(a)

a Not corrected for ties.

Table 10, above, shows the results of a Mann-Whitney U-Test which compares the prevalence rates of heavy schizophrenic smokers by gender and regardless of setting. Here there is a statistically significant difference ($p=0.01$) with male schizophrenics having a greater rate of heavy smokers compared to female schizophrenics.

SECTION 2.3.5 Further analysis of data

Of the initial 50 studies there were 8 that gave data for mean number of cigarettes smoked with only 1 of these providing gender data for this. 4 studies gave data on when the patients studied developed schizophrenia with only 2 of these providing gender data. Details for this are given in table 11 with descriptive statistics in table 12.

Table 11 Studies with either mean cigarette per day (cpd) values or those which specified the age of onset of schizophrenia in study participants

Study	Setting	Mean cpd	Male mean cpd	Female mean cpd	Age of onset of schizophrenic illness	Age of illness onset in schizophrenic males	Age of illness onset in schizophrenic females
(Altamura AC., 2003)	OP	.	.	.	21.9	20.7	24.2
(Goff DC., 1992)	OP	28.9
(Hamera E., 1995)	OP	31.3
(Itkin O., 2001)	OP	.	.	.	26.6	25.7	27.5
(McCreadie RG., 2003)	OP	27
(Mori T., 2003)	OP	22.6	.	.	24.7	.	.
(Uzun O., 2003)	OP	24.9
(Beratis S., 2001)	MIX	31.5	33.5	26.3	.	.	.
(Glynn SM., 1990)	MIX	21.8
(Akvardar Y., 2004)	MIX	.	.	.	23.5	.	.
(Ucok A., 2004)	MIX	34.5

Table 12 Descriptive statistics for data in table 11

	Number of studies	Minimum	Maximum	Mean	Standard Deviation
Onset age of schizophrenia	4	21.9	26.6	24.175	1.9822
Onset age of schizophrenia for males	2	20.7	25.7	23.200	3.5355
Onset age of schizophrenia for females	2	24.2	27.5	25.850	2.3335
Mean cigarettes smoked per day	8	21.8	34.5	27.815	4.5398
Mean cigarettes smoked per day by male schizophrenics	1	33.5	33.5	33.500	.
Mean cigarettes smoked per day by female schizophrenics	1	26.3	26.3	26.300	.

As is to be expected from previous research (Hafner H., Riecher A., Maurer K., *et al*, 1989), even with a small number of studies, the mean onset age for schizophrenia was lower in males (mean 23.2 years) than in females (25.85 years) by 2.65 years. From the four studies that had data for the age of onset of illness the mean age of onset, irrespective of gender, was 24.18 years.

Only one study had data comparing the mean cpd by gender which showed that males smoked more (mean cpd of 33.5) than females (mean cpd of 26.3). A total of eight studies reported mean smoking levels and the mean of these results was 27.8 cpd.

SECTION 2.3.6 SUMMARY OF RESULTS

1. The mean value for the rate of ever smokers in the studies found (n=50) in the systematic review was 66%.
2. A non-significant result was found showing that there was a tendency for inpatients (72%) with a diagnosis of schizophrenia to smoke more than their outpatient counterparts (64%) with the figure lying at 66% for those studies which had mixed inpatient and outpatient group. These differences were not statistically significant.

3. Male schizophrenic patients had a significantly higher prevalence rate of ever-smoking status ($p=0.04$) compared to female schizophrenic patients but this did not hold true when the results were examined by setting.
4. There was evidence that males (84% of outpatient smokers, 56% of inpatients smokers) smoked more heavily than their female counterparts (79% of outpatient smokers, 49% of inpatients smokers) and this result was statistically significant if the setting of the study was disregarded ($p=0.01$).
5. There was some evidence, again not significant, suggesting that of the outpatients who smoked they had a higher rate of heavy smoking compared to the inpatient group.
6. From a limited number of studies (table 12) there were as expected results showing that males' onset age for schizophrenia was lower than females.

SECTION 2.4.1

DISCUSSION OF SYSTEMATIC REVIEW RESULTS

SECTION 2.4.2

HYPOTHESIS 1 - Patients with Schizophrenia Who Are Inpatients Will be More Likely to be Smokers than their Outpatient Counterparts

This question was based on the premise that schizophrenic patients who were currently being managed within a hospital setting would be more unwell than those patients who were managing to live within the community. This hypothesis was rejected as there was no statistical difference between inpatient ($n=26$) or outpatient ($n=15$) study groups in terms of the prevalence rate of ever smoking. There was however a higher mean value of ever smokers in the inpatient group (72%) compared with the outpatient group (64%) with mixed setting ($n=9$) studies lying between these values at 66%.

SECTION 3.4.3 HYPOTHESIS 2 - Male Patients with Schizophrenia Will Have a Higher Prevalence Rate of Smoking Compared with Female Patients.

Worldwide data regarding the gender differences in smoking prevalence has consistently shown that males have a higher rate of smoking (42%) than females (12%) (World Health Organisation, 2003). This hypothesis was mooted in response to these figures to ascertain whether this followed suit in the schizophrenic population. In total 13 studies were identified across 3 settings which had prevalence rates which could be examined by gender (Table 6). When examined by individual setting there was a difference between genders with females proving to be consistently less likely to be smokers though it was clearly not statistically significant.

When the 3 settings were aggregated and the prevalence rates compared only by gender (Table 7) there was a statistically significant difference ($p=0.04$) between male and female schizophrenics with the former having a higher rate which allowed this hypothesis to be accepted. This is in keeping with global data however both male and female groups far exceeded the WHO statistics described above with the mean rate for schizophrenic men at 68.7% (s.d. 13.1%) and schizophrenic women at 47.2% (s.d. 26.4%).

SECTION 2.4.4 HYPOTHESIS 3 - Schizophrenic Smokers Will Have a Higher Prevalence Rate of Being Heavy Smokers than Normal Smokers

Unfortunately due to a paucity of control data within these studies the author was unable to give a direct comparison between the normal and schizophrenic populations for this question. However if a comparison is made between the total mean prevalence rate of smokers who smoke more than 20 cpd (i.e. are heavy

smokers) and the prevalence rate found in studies looking at the normal population there is a marked difference between the 2 groups.

The mean heavy smoking rate from this systematic review (Table 9) was 68% in males, 61% in females with a combined rate of 53%. As a comparison a general population study conducted during 2001 in the north-west of England (Frank PL., Morris JA., Frank TL., *et al*, 2004), which has the highest rate of smoking in the UK (Walker A., Maher J., Coulthard M., *et al*, 2001), found heavy smoking prevalence rates (as a proportion of total rates of ever smokers) to be 38.4% in males and 30.1% in females. The latter figures demonstrate that there may well be a higher prevalence rate of heavy smokers within the schizophrenic population though this answer is given tentatively in view of there not being a direct case-control study method applied.

As an addendum to this part of the review it is important to note the non-significant difference when heavy smoking within the schizophrenic population was analysed by setting.

SECTION 2.4.5 HYPOTHESIS 4 - Male Schizophrenic Smokers Will Have a Higher Prevalence Rate of Being Heavy Smokers Compared to Female Schizophrenic Smokers

This question was raised in the light of studies which have reported males to be more likely to be heavy smokers than females within normal populations (Frank PL., Morris JA., Frank TL., *et al*, 2004). The hypothesis was confirmed with the same result holding true within the schizophrenic populations analysed with males having a higher prevalence rate of heavy smoking in comparison to females (Table 10, $p=0.01$).

SECTION 3

A META-ANALYSIS OF CASE-CONTROL STUDIES EXAMINING THE PREVALENCE OF SMOKING IN SCHIZOPHRENIA

SECTION 3.1.1 INTRODUCTION

Although the systematic review results have shown with some clarity the increased prevalence rates of cigarette smoking amongst schizophrenic populations both in and out of hospital; the question as to how this compares with smoking in the normal population still remained to be answered. This would allow a description of the amount of risk that being a cigarette smoker confers on being schizophrenic also.

To allow an adequate representation of this comparison it was felt appropriate to compile a meta-analysis from the case-control studies that had been found, in the most part, from the systematic review. This had initially been intended to include case-control studies which had had schizophrenic patients smoking rates compared with both normal and other psychiatric diagnoses control groups however there were insufficient numbers of the latter type of study to allow for meaningful statistical analysis with this technique.

SECTION 3.2.1 METHODS

SECTION 3.2.2 Study Selection

From the original set of 50 papers that had been obtained by the process of systematic review (Table 17) there were 5 (De Leon., 2002) (Herran A., Santiago A., Sandoya M., *et al*, 2000) (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986)

(Lyons MJ., Kremen WS., Eisen SA., *et al*, 2002) (McReadie RG., 2002) that were able to be examined in a meta-analysis due to the presence of a control group. The remaining 45 studies had no control group or no extractable control data. In addition to these 5 studies a further 6 were discovered by using identical search criteria as those in section 2.2.2 of the systematic review. The characteristics of each of these schizophrenic and control groups are outlined in Table 13.

Table 13 Descriptive table outlining the features of the studies found in the systematic review that were included in the meta-analysis.

Study	Setting	Country	How was current smoking determined	How was schizophrenia diagnosed	Characteristics of Control group
(Beratis S., 2001)	MIX	Greece	Smoked >100 cigarettes and still smoking (or only quit in last month)	DSMIII-R / IV	Age/Sex/Setting all matched Occupation/Education most matched
(De Leon J., 2002)	IP	USA	Questionnaire/FTND	DSMIV	>18yo, Community sample
(De Leon., 2002)	IP	USA	Questionnaire/ERBS	DSMIII-R	Non-schizophrenic psychiatric pts
(Degenhardt L., 2001)	OP	Australia	Questionnaire	CIDI (DSMIII-R)	Community sample
(Herran A., 2000)	OP	Spain	Questionnaire/FTND	DSMIV	24-44yo subjects from (Diez-Manrique JF., 1996)
(Hughes JR., 1986b)	OP	USA	Questionnaire	DSMIII	Community sample
(Lyons MJ., 2002)	OP	USA	DSMIII-R	DISII-R	VET registry
(McCreadie RG., 2002)	OP	Scotland	Questionnaire	ICD-10	Age/Sex/Postcode matched
(Calabresi M., 1991)	MIX	Italy	Questionnaire	Unknown	Non-schizophrenic psychiatric patients
(Ucok A., 2004)	MIX	Turkey	Regular smoking every day for >1 month	SCID	Healthy relatives of neurological dept outpatients
(Riala K., 2005)	MIX	Finland	Questionnaire	DSMIII-R	Healthy controls from Northern Finland 1966 Birth Cohort

OP – Outpatient populations

IP – Inpatient populations

Mix – Mixed populations with n's provided where given in studies

DSM – Diagnostic Statistical Manual of Mental Disorders (version indicated by roman numerals)

ICD – International Classification of Diseases (version indicated by integer)

SCID - The Structured Clinical Interview for DSM-IV

FTND – Fagerstrom Test of Nicotine Dependence

ERBS – Elgin Repetitive Behaviours Scale

CIDI – Composite International Diagnostic Interview

DISIII-R – Diagnostic Interview Schedule Version III-Revised

VET Registry – Vietnam Era Twin registry

SECTION 3.2.3 Data Extraction

For studies to be included in the meta-analysis a set of entry criteria was applied which was the same as for the initial review (see section 2.2.3) with an additional clear focus on comparing the prevalence rates of current smoking among control groups as well as adult schizophrenic populations, as defined by operationalised criteria (except in the case of (Calabresi M., Casu G. & Dalle Luch R., 1991) where no criteria was able to be found within the paper). In addition studies had to include data for the total number of subjects in each group as well as the total number of current smokers within each group.

Quantitative data extracted from retrieved articles included both data to allow assessment of potential sources of heterogeneity for example age, gender, illness characteristics, family history and other lifestyle factors such as use of drugs or alcohol. Where possible, data was tabulated for the amount smoked by the subjects and what proportion of them smoked. This allowed for the calculations detailed in Table 14, below.

SECTION 3.2.4 Statistical Analysis

SECTION 3.2.4a Effect size

STATA software was used for all data storage and statistical analyses. Estimates of Odds Ratios and their variance were estimated using the Mantel-Haenszel method. Subgroup and overall estimates of effect size were estimated using random effects meta-analysis by using the DerSimonian and Laird moment-based estimator of between-study variance. The direction of the effect size was negative if the schizophrenic group had a lower prevalence of smoking when compared to controls.

SECTION 3.2.4b Heterogeneity of Effect Size

Heterogeneity of effect sizes was tested using the Q statistic, with $P < 0.10$ as the cut off level of significance. Because tests of heterogeneity may be underpowered if the number

of studies is small, we also explored its magnitude using the I-squared statistic. This quantity estimates the percentage of total variation across studies due to heterogeneity. Meta-regression was used to explore age and gender effects for any variable which showed greater than 20% of variation in effect size due to heterogeneity.

The summary statistics show that a random effects analysis was employed due to there being significant heterogeneity between the studies which also negated the problems that can be associated with fixed effects modelling, namely the assumption that each study is an estimate of a single underlying effect rather than assuming that all included studies are a true random sample of all possible studies. (Lawrie SM., McIntosh A. & Rao S., 2000).

SECTION 3.2.4c Publication Bias

Publication bias was assessed graphically using funnel plots of standardised mean difference versus its standard error. The Egger test was used to formally test for the presence of publication bias, by estimating the intercept of the regression line fitted to Galbraith Radial Plot.

SECTION 3.3.1 RESULTS

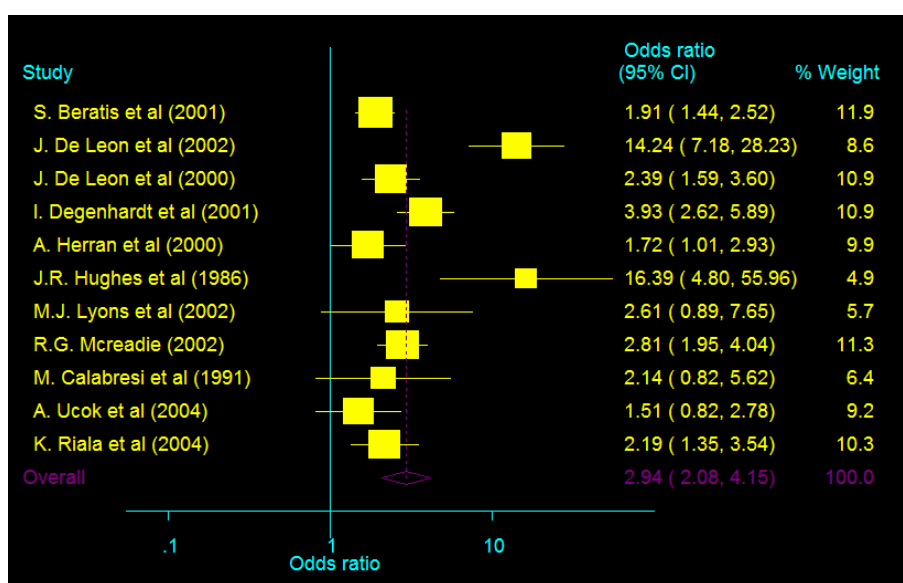
Table 14 Data extraction from 11 studies used in the meta-analysis with results of the same included

Study	Total Number of Schizophrenic Patients	Total Number of Controls	Number of Schizophrenic Smokers	Number of Control Smokers	Odds Ratio	95% Confidence Interval	Percentage Weight
(Beratis S., 2001)	406	406	237	172	1.908	1.44 - 2.52	11.89
(De Leon J., 2002)	66	404	55	105	14.238	7.18 – 28.23	8.55
(De Leon., 2002)	449	127	335	70	2.393	1.59 – 3.60	10.91
(Degenhardt L., 2001)	99	6722	59	1835	3.928	2.62 – 5.89	10.95
(Herran A., 2000)	64	710	41	361	1.723	1.01 – 2.93	9.87
(Hughes JR., 1986b)	24	411	21	123	16.39	4.80 – 55.96	4.9
(Lyons MJ., 2002)	24	3347	20	2199	2.61	0.89 – 7.66	5.72
(McCreadie RG., 2002)	250	250	162	99	2.808	1.95 – 4.04	11.28
(Calabresi M., 1991)	71	29	57	19	2.143	0.82 – 5.62	6.43
(Ucok A., 2004)	66	114	38	54	1.508	0.82 – 2.78	9.18
(Riala K., 2005)	67	8041	32	2369	2.189	1.35 – 3.54	10.3
D and L Pooled Odds Ratios					2.940	2.08 – 4.15	100.00

The following bullet points provide the summary statistics for the meta-analysis

- Heterogeneity chi-squared = 47.55 (d.f. = 10) $p = 0.000$
- I-squared (variation in OR attributable to heterogeneity) = 79.0%
- Estimate of between-study variance Tau-squared = 0.2404
- Test of OR=1 : $z = 6.13$ $p = 0.000$

Figure F Forrest Plot from meta-analysis data described in table 28



Of all 11 studies only 3 have confidence intervals which at the lower end are less than 1 ((Lyons MJ., Kremen WS., Eisen SA., *et al*, 2002) (Calabresi M., Casu G. & Dalle Luch R., 1991) (Ucok A., Polat A., Bozkurt O., *et al*, 2004) that is to say are not statistically significant. The first of these studies (Lyons MJ., Kremen WS., Eisen SA., *et al*, 2002) may show less of an effect due to the small sample size of the schizophrenic population though this was not a factor for another of the studies with the same 'n' (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986) in addition there is a higher prevalence rate of smoking in the control group (65.7%) of the former study. The work of (Calabresi M., Casu G. & Dalle Luch R., 1991) has a control group of non-schizophrenic psychiatric outpatients who have a higher prevalence rate of smoking (65.51%) than the normal control groups used in the majority of the other studies range (25.9% - 50.8%) which will reduce the odds ratio. The final non-significant result was from the Turkish study (Ucok A., Polat A., Bozkurt O., *et al*,

2004) which states itself that there is a higher prevalence rate of smoking in the normal population than in other countries which affected their, and hence my, results. There are 2 outliers which show a more dramatic pattern of risk associated with cigarette smoking (De Leon J., Diaz FJ., Rogers T., *et al*, 2002; Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986) with odds ratios of 14.24 (95%CI 7.18 - 28.23) and 16.39 (95%CI 4.80 – 55.96) respectively. The former study appears to have no obvious explanation for the larger odds ratio especially in view of its relatively large sample size of the schizophrenic population (n=449) and the authors' themselves provide no insight into why it might be high. The second study (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986) actually states that their results may be an underestimate of the amount of smokers in their schizophrenic population as self-reported prevalence is usually an underestimate of the true prevalence.

SECTION 3.3.2 SUMMARY OF META-ANALYSIS RESULTS

1. The D and L pooled odds ratio for this meta-analysis (n of studies=11) was found to be statistically significant. The value for the odds was high at 2.94 (C.I. 2.08 – 4.15) .

SECTION 3.4.1**DISCUSSION OF META-ANALYSIS RESULTS****SECTION 3.4.2 HYPOTHESIS 5 - Schizophrenic Patients are Significantly More Likely to be Cigarette Smokers than Individuals in the Well Population**

This question was posed to answer more conclusively that which has been suggested for years that there is an association between cigarette smoking and schizophrenia. From the results of the meta-analysis it is clearly shown that suffering from schizophrenia carries with it a significantly greater odds of being a current cigarette smoker than being a non-smoker ($p < 0.00$).

The actual elevation in the probability of being an ever smoker is demonstrated by a pooled odds ratio of 2.94 (95% CI 2.08 – 4.15) which equates to an almost 3 fold increase in that risk. The possible reasons behind these significantly raised odds will be elucidated in the synthesis below.

SECTION 4

AN INVESTIGATION INTO PATTERNS OF CIGARETTE SMOKING IN SCHIZOPHRENIA USING DATA FROM THE EDINBURGH HIGH-RISK STUDY

SECTION 4.1.1 Introduction

SECTION 4.1.2 What is the High-risk Study and how can it answer my questions?

As has been outlined in the introductory section there is an increasing amount of compelling evidence for schizophrenia being a neurodevelopmental disorder of the brain (Weinberger DR., 1995). Direct evidence of this being the aetiology as well as establishing what might be the various risk factors that could point to what causes the developmental problems leading to schizophrenia requires a comparison between a normal control group and a group at a higher risk of developing the illness prior to its actual onset. With the lifetime risk of developing schizophrenia placed at around 1 percent (Jablensky A., 1995) it is too infrequent to be pragmatically studied by using general population samples. It is, however, more practical to study individuals whose relatives have schizophrenia due to the increased odds ratio of them developing the illness being put at 16.2 (Kendler KS. & Gardner CO., 1997).

In addition such studies allow for phenotypic and behavioural markers to be identified and, ultimately, therapeutic actions to be identified.

Previous prospective studies have had difficulties due to using infants of mothers with schizophrenia as there is a long wait between infancy and the subjects entering the period of being at most risk of developing the illness (Cornblatt B., 1997) most notably with the problems of high attrition in the study sample, problems with power calculations and dating of sampling instruments.

The EHRS is, like the other High-risk studies, focussed on examining individuals who are at a greater genetic risk of developing schizophrenia but its design is different. It includes subjects who have at least 2 close relatives (defined as first or second degree) with schizophrenia but starts examining them from when they are in early adulthood thus eliminating the problems outlined above (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000). Subjects were drawn from areas throughout Scotland and were drawn from an age range of between 16 to 25 years old ensuring that the study period is during the time of maximal risk of developing the illness. Initially it had been planned to follow them every 18 to 24 months over a 5 year period, as this was felt to allow interpretable numbers for the study to be gained due to the relatively narrow age of onset, or until they developed a clinically diagnosed psychotic illness. The study time has been lengthened as the follow-up work is still ongoing to this day (Johnstone EC., Miller P., Ebmeier KP., *et al*, 2005).

The study is primarily organised and conducted from the University of Edinburgh's Division of Psychiatry based at the Royal Edinburgh Hospital (Hodges A., Byrne M., Grant E., *et al*, 1999).

The EHRS has afforded the author the opportunity of comparing whether and how much members of the 4 groups smoke; those with symptoms who are at 'high risk' of developing schizophrenia, those without symptoms who are at 'high risk', those who are normal controls and those who are schizophrenic controls. It also allows observation of at what points smoking rates change in the various samples. This should give answers to some of the questions and hypotheses outlined in sections 1.7.1 and 1.7.2 and provide some idea of the line of causation between the illness and consumption of cigarettes.

SECTION 4.2.1 METHOD

SECTION 4.2.2 Recruitment

When the study was first started it had been hoped that the requisite number of subjects to make the study viable would be available within Lothian. Unfortunately sufficient numbers of young people with families multiply affected with schizophrenia were unavailable so a number of other centres were established including Argyll and Clyde, Highlands and Islands, Dumfries and Galloway, Borders, Forth Valley and Perth (Hodges A., Byrne M., Grant E., *et al*, 1999).

As stated above subjects in the 'high risk' arm were required to have 2 close relatives with a diagnosis of schizophrenia which was made, where possible, using the Operational Criteria Checklist (McGuffin P., Farmer A. & I., 1991). Such families were found by examining psychiatric case notes of all patients with schizophrenia in individual hospitals. If there was data suggestive of the patient having a close relative affected with the illness then consent was obtained from that patient to have a healthy relative contacted. This person then was asked to detail a full familial psychiatric history with specific focus on whether there was a close relative to the patient aged between 16 and 24 years old.

Permissions were sought throughout from involved clinical teams and relevant medical practitioners. Care and tact were clearly required when dealing with issues of familial psychiatric illness particularly when approaching individual young people who may not have been aware of their increased risk of developing schizophrenia. Initiation was, therefore, often through an older healthy relative (Hodges A., Byrne M., Grant E., *et al*, 1999).

In total over 2500 sets of case files were reviewed and approximately 500 home visits were made to patients and their families (Hodges A., Byrne M., Grant E., *et al*, 1999). By the end of the recruitment period in July 1999, some 229 high risk

participants were ascertained. Of these 163 had provided some data and 156 provided complete data (Johnstone EC., Miller P., Ebmeier KP., *et al*, 2005). From what is already known about the rates of illness within such families it was expected that between 20 and 30 would go on to develop schizophrenia (Kendler KS., McGuire M., Gruenberg A., *et al*, 1993). This approximate figure was used to establish how large the other groups would need to be for statistical analysis.

As well as the above arm, two further control samples were recruited for the EHRS. The well control group were recruited from the social network of the high risk individuals themselves. This enabled an improvement in matching for age and socio-economic status. They had to have no personal or family history of psychotic illness but they could have second-degree relatives with other psychiatric illnesses (Hodges A., Byrne M., Grant E., *et al*, 1999). Beyond these criteria they were as similar as possible to the high risk subjects (Johnstone EC., Miller P., Ebmeier KP., *et al*, 2005). 36 were eventually found and given the same battery of assessments over time as the high-risk portion (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000).

The second control group was comprised of first-episode schizophrenic patients enlisted from local hospitals in Scotland and were balanced group-wise for age and sex with the high risk individuals. In contrast to the other two groups the first-episode arm subjects were only assessed at the first meeting (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000).

All the above was centred around enabling a comparison to be made between the premorbid states of the high-risk group who go on to develop psychosis, those who remain well and the two control groups thus allowing a delineation of variables which could provide clues about how the illness develops.

SECTION 4.2.3 Data Collection

The clinical, social and demographic information described within this study was collected from all the subjects at face-to-face interviews. Initially the Schedule for

Affective Disorders and Schizophrenia – Lifetime (SADS-L) (Spitzer RL., Williams VBW., Gibbon M., *et al*, 1987) was used to determine life-time psychopathology in the subjects. As stated in (Hodges A., Byrne M., Grant E., *et al*, 1999) the familial history of psychiatric disorder had been established by interviewing subjects' relatives as part of the recruitment procedure.

A developmental history, as well as establishing the presence of obstetric complications, was obtained by interviewing both the subjects and their mothers at length. This included questions about school career, social work involvement and periods in foster care. In addition to this a more general enquiry was carried out into the participants' psychological and physical states. The primary tool for assessing psychopathology was the Present State Examination (PSE) (Wing JK., Cooper JE. & Sartorius N., 1974); this battery was carried out at entry, if the person presented to clinical services with the possibility of developing a psychiatric illness and at subsequent return interviews (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000). The PSEs were not all videotaped due to the suspicions this aroused in some of the subjects who were becoming psychotic but were carried out usually apart from this to allow a clear definition of the development of schizophrenia on clinical and PSE / CATEGO grounds (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000).

From the PSE data a five point scale for psychopathology was developed (table 14) (Johnstone EC., Abukmeil SS., Byrne M., *et al*, 2000).

Table 14 Five point scale for psychopathology in the EHRS

Score	Symptoms
0	No psychotic or neurotic symptoms
1	Neurotic symptoms only
2	Partially held psychotic symptoms
3	Definite but isolated and/or transient psychotic symptoms
4	Schizophrenia as diagnosed by ICD-10(World Health Organisation, 1992)

Psychotic illness of a non-schizophrenic nature is not covered by the above scale but did not occur in any case. Those with a score of 2 or 3 were combined into one

group, high risk with positive evidence of schizophrenic symptoms (HR+), and are referred to as having had psychotic or possibly psychotic symptoms (Johnstone EC., Miller P., Ebmeier KP., *et al*, 2005). This allowed a division and comparison between 4 groups for the purposes of the study.

1. Normal Controls.
2. High-risk subjects with no psychotic symptoms (HR-).
3. High-risk subjects with psychotic symptoms (HR+)
4. First episode schizophrenic patients.

To obtain the data on the presence and quantity of cigarettes smoked I was granted access to the initial and return assessments for all these groups. I was blind at this stage to which groups the subjects were in and this remained the case until the data analysis was complete. From discussion with the interviewers, patients were asked as to whether they smoked and, if so, how many cigarettes were smoked per day.

The recording of cigarette usage was not always present within the case records and these portions of the data set were left blank and unanalysed. Of the majority that did have answers there were variable ways in which the data was written down. To enable statistical analyses to be made a scale was developed to allow a cohesive grouping of the data. This broke down into 5 groups

1. Never/rarely smoked.
2. Ever smoked.
3. 1-10 cigarettes per day (CPD) smoked.
4. 10-20 CPD smoked.
5. 20 or more CPD smoked.

This process was repeated for the return assessments which were done to allow any change over time between the groups to be entered into the data set and analysed.

SECTION 4.2.4 Data Analysis

Throughout the results section for the work completed within the Edinburgh High-risk Study the author used the Statistical Package for Social Sciences (SPSS) Version 12.0 for Windows. Due to the nature of the data obtained non-parametric tests of significance were employed as the data was not normally distributed. Normality was assessed in all cases by using the Shapiro-Wilk test.

Results for smoking have been recorded as ever or never smoking. The ever smoking group included those subjects who were current smokers also. This allowed for the clearest description of the data. Unfortunately there was variable recording of the actual quantity of cigarettes smoked per day in the assessment papers used for each subject at the various time points. This variation could not furnish enough detail for meaningful data analysis and is a matter the author will address in my discussion of the results.

SECTION 4.3.1 RESULTS

SECTION 4.3.2 Analyses of EHRS Data Comparing All Groups at the First Assessment Point

Table 15, below, shows the prevalence rates of ever smoking for all the subjects in the study, where data was available barring those patients who were schizophrenic controls. Analysis of this data, shown in table 16, shows there is a non-significant ($p=0.18$) difference between those subjects who were at high risk of developing schizophrenia who had psychotic symptoms at the first assessment point to have ever smoked compared to those who in the same group who had not developed psychotic symptoms by this point or those in the normal control group.

Table 15 A comparison of the rates of smoking between the control group and the high risk groups divided into those who did and did not have psychotic symptoms at the 1st time point

			Ever smoked		Total
			Never	Ever	
Group	High risk -ve	Count	77	51	128
		% within Group	60.2%	39.8%	100.0%
	High risk +ve	Count	7	11	18
		% within Group	38.9%	61.1%	100.0%
	Control	Count	23	13	36
		% within Group	63.9%	36.1%	100.0%
Total		Count	107	75	182
		% within Group	58.8%	41.2%	100.0%

Table 16 Pearson Chi-Square analysis of data from table 15 which demonstrates non-significant difference for high risk subjects with psychotic symptoms to be an ever smoker than high risk subjects without symptoms or the control group

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.43	2	0.18
Likelihood Ratio	3.37	2	0.19
Linear-by-Linear Association	0.00	1	0.99
N of Valid Cases	182		

0 cells (.0%) have expected count less than 5. The minimum expected count is 7.42.

Figure E, below, allows for a more clear graphical representation of the differences in ever smoking prevalence rates between the high risk with symptoms group, high risk without symptoms group and control group at the first assessment point.

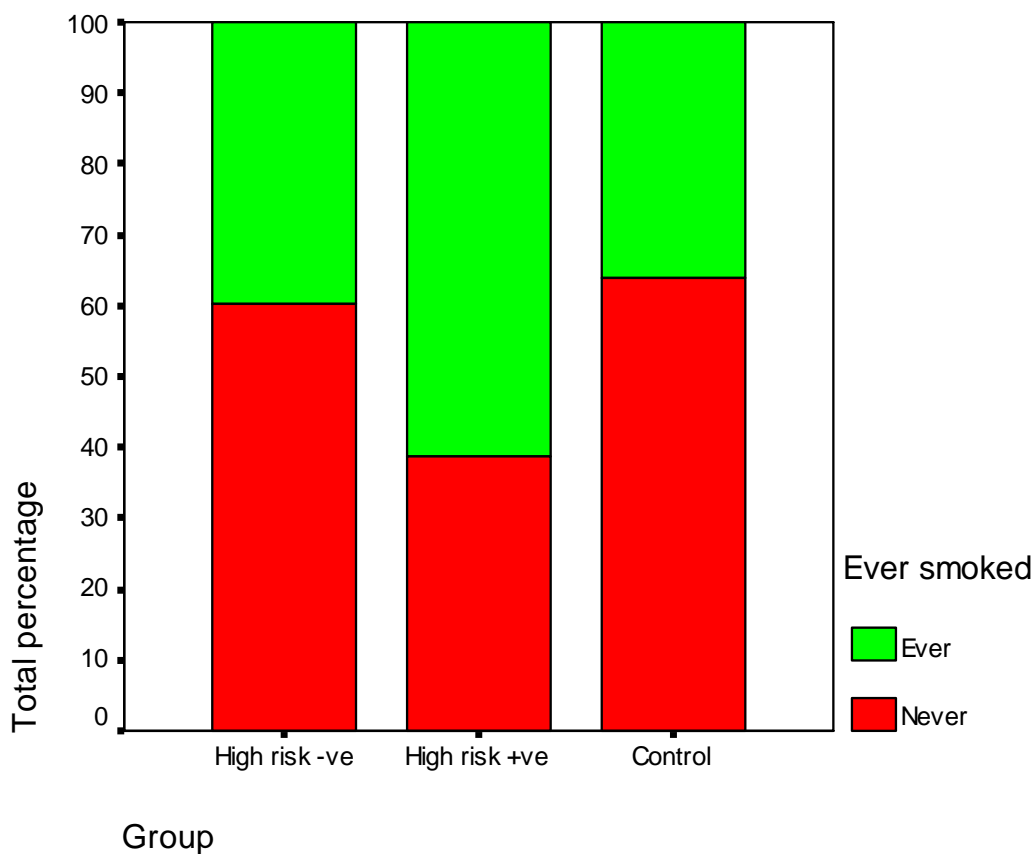
Figure E - Bar chart illustrating data from table 1

Table 17, below, shows the results of a statistical analysis comparing those in the high risk group for schizophrenia without psychotic symptoms to the normal control group. There is clearly no statistically significant difference between these two groups ($p=0.69$) in terms of their smoking status at the first time they were assessed.

Table 17 Mann-Whitney test data showing no significant difference when comparing numbers of subjects who ever smoked in HR- group compared to control group at 1st time point

Ranks				
	Group	N	Mean Rank	Sum of Ranks
Ever smoked	High risk -ve	128	83.17	10646.00
	Control	36	80.11	2884.00
	Total	164		

Test Statistics

	Ever smoked
Mann-Whitney U	2218.00
Wilcoxon W	2884.00
Z	-.40
Asymp. Sig. (2-tailed)	.69

The following data set (Table 18) shows that there is a trend, which did not reach statistical significance ($p=0.09$), for those who had psychotic symptoms in the high-risk group to be ever smokers compared with those without such symptoms in the high-risk group at the first time point to have ever smoked. The crude unadjusted odds ratio for this result is 2.3725 with 95% confidence intervals of 0.9 to 6.5. The power is represented by the width of the 95%CI.

Table 18 Chi-square test data showing a trend, but no significant difference, towards subjects in the HR+ group having a higher rate of ever smoking compared with the HR- group

	Group	N	Never	Ever
Ever smoked	High risk –ve	128	77	51
	High risk +ve	18	7	11
	Total	146		

Test Statistics

	Ever smoked
Pearson Chi square	2.921
Df	1
Asymp sig	0.087
N of cases	146

Table 19, see below, illustrates the results of a Mann-Whitney U test comparing the prevalence rate of ever smoking in the high-risk group with psychotic symptoms compared with those in the well control group. This shows a trend, although not statistically significant ($p=0.08$), for those in the HR+ group to have ever smoked at the time of the first assessment compared to those who were well and not at a high genetic risk of developing schizophrenia.

Table 19 Mann-Whitney test data showing no significant difference, but greater evidence of a trend compared to table 5's chi-square analysis, for HR+ subjects to be ever smokers compared to the control group

Ranks				
	Group	N	Mean Rank	Sum of Ranks
Ever smoked	High risk +ve	18	32.00	576.00
	Control	36	25.25	909.00
	Total	54		

Test Statistics	
	Ever smoked
Mann-Whitney U	243.00
Wilcoxon W	909.00
Z	-1.72
Asymp. Sig. (2-tailed)	.08

Table 20 is a descriptive frequency table comparing the three initial broad groups with no subdivision of the high-risk set by symptomatology or consequent outcome. This data has been used for analysis in table 21.

Table 20 Frequency table for all the high-risk subjects irrespective of outcome, controls and first episode schizophrenic patients for ever smoking rates at 1st round screening

			First round smoking		Total
			No	Yes	
Group	High risk	Count	84	62	146
		% within Group	57.5%	42.5%	100.0%
	Control	Count	23	13	36
		% within Group	63.9%	36.1%	100.0%
	Schizophrenic	Count	6	17	23
		% within Group	26.1%	73.9%	100.0%
Total		Count	113	92	205
		% within Group	55.1%	44.9%	100.0%

The following Pearson Chi-Square test (table 21) has been performed on the data from table 20. It shows that schizophrenic patients were significantly more likely to

have been ever smokers ($p=0.01$) than either the high-risk group as a whole or the control group.

Table 21 Chi-Square test comparing all the high risk subjects irrespective of outcome with controls and first episode schizophrenic patients for ever smoking rates at 1st round screening (see table 9). This demonstrates a significantly higher presence of smoking amongst the 1st episode schizophrenic patients with no difference between the high risk and control subjects

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.30(a)	2	.01
N of Valid Cases	205		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 10.32.

SECTION 4.3.3 Analyses of EHRS Data Comparing All Groups at the Fourth Assessment Point

The data set below (table 22) is a frequency table showing the number and associated percentage values for the full high-risk group (irrespective of outcome or symptom profile) and the control group at the fourth round of assessments.

Table 22 Frequency table for all the high risk subjects irrespective of outcome and controls for ever smoking rates at 4th round screening

			Fourth round smoking		Total
			No	Yes	
Group	High-risk	Count	40	18	58
		% within Group	69.0%	31.0%	100.0%
	Control	Count	17	3	20
		% within Group	85.0%	15.0%	100.0%
Total		Count	57	21	78
		% within Group	73.1%	26.9%	100.0%

Table 23 shows the results of a Pearson Chi-Square analysis of the data from table 22. This shows that there continues to be stability of there being no statistically significant difference between the whole group of those who were at high risk of developing schizophrenia compared with the normal control group for being ever smokers. It does, however, demonstrate a non-significant difference for the high-risk group to have been ever smokers ($p=0.16$).

Table 23 Chi-Square test comparing all the high-risk subjects irrespective of outcome and controls for ever smoking rates at 4th round screening (see table 11). This demonstrates stability over time of there being no significant difference between the control and high-risk groups for ever smoking

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.94(b)	1	.16
N of Valid Cases	78		

b 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.38.

SECTION 4.3.4 Analyses of EHRS Data Using the High-Risk Group Data When Divided into Those Who Did and Did Not Go on to Develop Schizophrenia

Table 24, below, gives a description of ever smoking rates, in terms of numbers in the groups as well as the corresponding percentages, for the normal control group in comparison with the high-risk group. The latter group has, however, been divided into those who went on to eventually develop schizophrenia by the fourth assessment period. This allows for the two comparison analyses illustrated in Tables 25 and 26.

Table 24 A comparison of the rates of ever smoking between the control group and the high-risk groups divided into those who did and did not develop schizophrenia by the 4th time point

			First round ever smoking		Total
			No	Yes	
Group	High risk subjects who did not develop schizophrenia	Count	80	51	131
		% within Group	61.1%	38.9%	100.0%
	Control group	Count	23	13	36
		% within Group	63.9%	36.1%	100.0%
	High risk subjects who did develop schizophrenia	Count	7	11	18
		% within Group	38.9%	61.1%	100.0%
Total		Count	110	75	205
		% within Group	59.5%	40.5%	100.0%

Table 25 is a Pearson Chi-Square analysis of the three groups delineated in table 24. This shows there is a result, which was not statistically significant though approaches a trend ($p=0.11$), for the portion of the high-risk group who developed schizophrenia to be more likely to have been ever smokers at the first assessment point compared with those who did not develop schizophrenia or the control group.

Table 25 A comparison of the rates of smoking between the control group and the high-risk groups divided into those who did and did not develop schizophrenia by the 4th time point

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.59	2	.11
N of Valid Cases	185		

The below Pearson Chi-Square analysis (table 26) is comparing only those subjects who were at high risk of developing schizophrenia when divided into a group who did go on to develop schizophrenia compared to a group who did not go on to become schizophrenic. This shows a trend, though again not reaching true statistical significance ($p=0.07$), for those at high-risk who went on to become unwell to have been ever-smokers at the first time they were assessed for the EHRS.

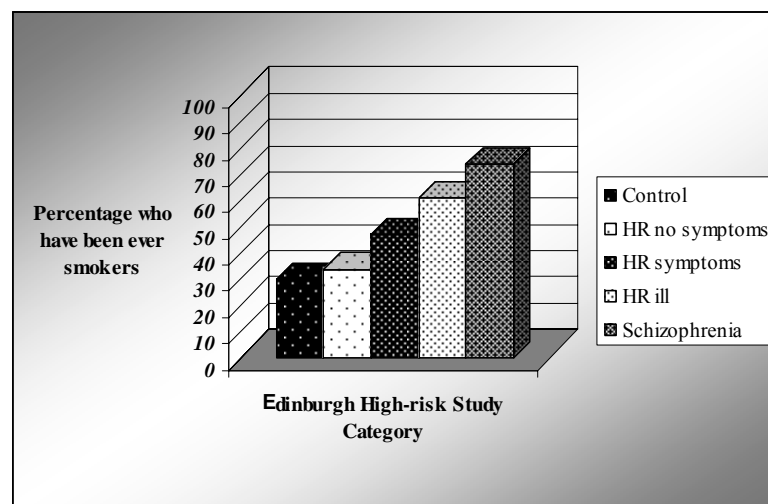
Table 26 A Chi-Square comparison of the rates of smoking between the high-risk groups only, divided into those who did and did not develop schizophrenia, by the 4th time point showing a strong tendency for those who developed schizophrenia to have ever smoked at the 1st round in comparison to those who did not.

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.20	1	.07
N of Valid Cases	185		

SECTION 4.3.5 Summary Of Ever Smoking Data at the First Assessment Point for All Possible Groups

The bar chart below (Figure H) gives a clear illustration of how there is a trend for an increased percentage of ever smokers by groups. Normal control subjects have the lowest rate of being ever smokers at the first assessment followed by those high-risk subjects who had no symptoms, then by those with symptoms, then by those who ultimately became ill and, finally, by the group who already had a diagnosis of schizophrenia.

Figure H - Bar Chart illustrating percentage of ever smokers within each possible group of the Edinburgh High-Risk Study, by both symptomatology and outcome, at the first assessment point.



SECTION 4.3.6 SUMMARY OF RESULTS

1. There is a non-significant difference ($p=0.18$) for the rates of ever smoking between the high-risk group members with psychotic symptoms when compared with those in the high-risk group without such symptoms or the well control group at the first assessment point. However there was evidence of a trend ($p=0.09$) when the high-risk group with psychotic symptoms was compared only with the high-risk group without psychotic symptoms or only with the control group ($p=0.08$) for rates of ever smoking. The crude unadjusted odds ratio for the former result is 2.3725 with 95% confidence intervals of 0.9 to 6.5. The power is represented by the width of the 95%CI.
2. There is no significant difference ($p=0.69$) for the high-risk group without psychotic symptoms and the control group in ever-smoking status at the first time point.

3. The schizophrenic control group were significantly more likely to be ever smokers at the first time point than both the high-risk and control groups ($p=0.01$).
4. At the fourth time point there continued to be no significant difference between those in the well control group and the high-risk groups for ever-smoking status ($p=0.16$).
5. When the high-risk group was divided into those who did and did not go on to develop schizophrenia there was a trend ($p=0.07$) for those who did become unwell to have been ever-smokers at the first time point.

SECTION 4.4.1 **DISCUSSION OF HIGH-RISK STUDY** **INVESTIGATION RESULTS**

SECTION 4.4.2 **Methodological Problems**

SECTION 4.4.3 **Recording of Cigarette Use**

As alluded to earlier, when the author states the prevalence rates of smokers this has been in terms of had the subject ever smoked or never smoked. This was unfortunately due to the variable way in which cigarette consumption was recorded by the initial researchers. Although this allows a clear delineation of the categories it does mean that intensity of smoking data is lost as well as the ability to establish how smoking patterns changed over time to some extent. This is because once patients have been recorded as an ever smoker, even if they quit, this status does not change. However this method of recording is in keeping with the largest and most recently

published meta-analysis of this subject (De Leon J. & Diaz FJ., 2005) and as such will allow comparison with previous author's results.

Future studies may be improved by having a shift of focus from recording the number of cigarettes smoked to establishing the subject's level of dependence on nicotine by using such instruments as the FTND (see table 27) which has been shown to be a valid measure of heaviness of smoking as measured by physiological and biochemical indices (Heatherton T., Kozlowski LT., Frecker RC., *et al*, 1991) as well as psychological measures (Dijkstra A. & Tromp D., 2002). This would allow a better investigation of the possible correlation between true dependence and schizophrenia rather than just using whether or not the patient has ever smoked that would thus allow a clearer examination of underlying abnormalities that may be present in both these problems.

Table 27 Items and scoring for the Fagerstrom Test for Nicotine Dependence (FTND)

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in the cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes per day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

SECTION 4.4.4 Heritability of Smoking as a Confound

As described in section 1.5.2, there is evidence for tobacco smoking behaviours to be at least partly inherited via the genotype. To eliminate this as a potential confounder it would have been necessary to take a familial smoking history and, if possible, perform the FTND on all the subjects' parents. Though this would not completely

eliminate the problem as it is suggested by some authors that schizophrenia and smoking behaviours may both occur due to a common shared genetic vulnerability within the subjects (De Leon J., 1996) (Stassen HH., Bridler R., Hagele S., *et al*, 2000).

SECTION 4.5.1 **Evaluation of Hypotheses**

SECTION 4.5.2 **Hypothesis 6 – The Schizophrenic Group in the Edinburgh High-Risk Study Will Have a Higher Prevalence Rate of Cigarette Smokers Compared with the Normal Population and High-Risk Groups**

From the data collated from within the Edinburgh High-Risk Study it was apparent that this hypothesis could be accepted. There was a clear ($p=0.01$, table 21) difference between the number of ever smokers in the schizophrenic group as compared to the control or high-risk groups at the first time point. This is in keeping with the results from my systematic review of the evidence base below and the author shall discuss the importance of this in that arm of the thesis' discussion section.

SECTION 4.5.3 **Hypothesis 7 – Patients at high-risk of developing schizophrenia will have a higher prevalence rate of cigarette smokers compared with the normal control group**

At the point of the first assessment this hypothesis must be rejected as there was no statistically significant difference between the high-risk and control groups. However there were clear trends demonstrated for the high-risk group with psychotic symptoms to have been ever smokers compared with the high-risk group without

symptoms ($p=0.09$, table 18) and compared with the control group ($p=0.08$, table 19). When the former result was further analysed it was found that the crude unadjusted odds ratio for this result is 2.3725 with 95% confidence intervals of 0.9 to 6.5. The power is represented by the width of the 95%CI.

At the fourth time of assessment the hypothesis continues to be rejected as there is a no difference between the whole high-risk group's rate of ever smoking compared to the control group ($p=0.16$, table 23). If the high-risk group is further divided into those who developed schizophrenia by this point compared with those who did not and the controls then a trend becomes evident ($p=0.10$, table 24). Furthermore if the comparison is limited to just the high-risk group who developed schizophrenia with those who did not develop schizophrenia then the significance becomes greater ($p=0.07$, table 26).

SECTION 4.5.4 SUMMARY

The most valuable result from this arm of the study may be the one that shows a trend ($p=0.07$) for those who were at high-risk and went on to become schizophrenic to have a higher prevalence rate of being ever smokers than their counterparts who stayed well even at the first time of assessment. This is because it suggests that there is a predictive value to determining whether or not someone has ever smoked if they are at a high genetic risk of developing schizophrenia. This would allow the clinician to make a reasonable, albeit not statistically significant, prediction that the individual concerned may go on to become unwell if they are an ever smoker who is already genetically predisposed to schizophrenia.

These results answer the first 2 questions posed in the introduction namely 'Are schizophrenics more likely to smoke than other groups?' and 'Are high-risk subjects more likely to smoke than their high-risk counterparts without symptoms?'. The final question is not wholly answerable from these results but if figure H is re-examined

then it can be seen that a preliminary affirmative answer is available to question 3, that is to say ‘does smoking correlate with illness severity?’, as the percentage of ever smokers in each group does show an almost linear progression with what could be regarded as ‘illness severity’ as there is a progression from normal controls through the high-risk no symptoms group, high-risk with symptoms group, high-risk who became ill group up to those who were schizophrenic at the first assessment.

The trend for the high-risk subjects who became schizophrenic to smoke more also suggests that something untoward is happening at the first assessment point, i.e. when they were not schizophrenic, which is leading them to smoke more cigarettes. The question of course is ‘what is the nature of this disturbance?’ and how cigarette smoking might alleviate or exacerbate it. The author will tackle this subject in the discussion section at the end of the thesis.

SECTION 5

SYNTHESIS AND DISCUSSION OF RESULTS

SECTION 5.1.1 SO WHY DO SCHIZOPHRENICS AND SOME OF THOSE WHO ARE AT HIGH-RISK OF DEVELOPING SCHIZOPHRENIA SMOKE MORE CIGARETTES THAN THE NORMAL POPULATION?

SECTION 5.2.1 THE BIOLOGICAL MODELS

SECTION 5.2.2 Cigarettes Improve Aberrant Information Processing Skills

As far back as 1962 it has been hypothesised that there may be a ‘schizotaxic factor’ (Meehl PE., 1962) which leads to the inherited predisposition to schizophrenia and may involve an increased level of neuronal sensitivity to sensory stimuli. Such information processing deficits may account for the symptomatic problems patients have in interpreting sight and sound leading to the disorder’s characteristic visual and auditory hallucinations (Leonard S., Adams C., Breese CR., *et al*, 1996).

The aforementioned factor has been preliminarily investigated in the work, outlined in section 1.3.1, involving the P50 auditory gating paradigm (Adler LE., Hoffer LD., Wiser BA., *et al*, 1993; Braff DL., Geyer MA., Light GA., *et al*, 2001) which has been shown to be defective in schizophrenic populations (Adler LE., Pachtman E., Franks R., *et al*, 1982) as well as their first degree relatives (Adler LE., Hoffer LD.,

Griffith J., *et al*, 1992). Adler's work showed that there was a significant reduction of the P50 gating ratio from >75% to 25% (normal subject value = 18%) in 5 minutes or less after the first cigarette smoking session however the effect was no longer significant after a second session (P50 ratio approximately 65%) (Adler LE., Hoffer LD., Wiser BA., *et al*, 1993). This problem is not repaired by the typical neuroleptic anti-dopaminergic drugs used to treat schizophrenia and as such cigarette smoking may represent an attempt by patients to treat it themselves (Adler LE., Olincy A., Waldo M., *et al*, 1998) and lead to the higher odds of them being smokers (OR=2.94) than the normal population as shown in section 3.3.2.

This deficit may be due to a disturbance within the hippocampus. Within this structure lie areas CA1-CA4 but it is the CA3 region particularly that is a major point of convergence for cortical and brain-stem inputs. It has been suggested (Hasselmo ME., Schnett E. & Barkai E., 1995) that the utility of this network depends on precise regulation (or gating) of the intensity of synaptic input to it which is felt to be mediated by cholinergic inputs. These may inhibit afferent inputs to CA3 and hence perform a gating function. Unfortunately Hasselmo *et al.* were not able to determine which cholinergic receptor is the basis for this effect but it has been postulated that the absence of cholinergic activity caused by a cholinergic receptor reduction in schizophrenia would result in perceptual difficulties as the affected person would constantly be altering autoassociative memory by overstimulation instead of recalling previous memories to place the new sensory input in the context of prior experience (Adler LE., Olincy A., Waldo M., *et al*, 1998). The most obvious candidate for this, as yet unidentified receptor, would seem to be the alpha-7 subtype of nAChRs which is known to be dysregulated in schizophrenia and alters sensory physiology (Leonard S., Gault J., Hopkins J., *et al*, 2002).

The increased prevalence of heavy smoking within the schizophrenic population, demonstrated by the acceptance of hypothesis 5, may also be tied in with this model. The alpha-7 nAChR is known to have a much lower affinity for nicotine than other subunits (alpha-2/3/4/5 and beta-2/3/4) (Seguela P., Wadiche J., Dinely-Miller K., *et al*, 1993). Most smokers, i.e. those within the general population who are not trying to

self-medicate for attentional deficits, probably use nicotine to stimulate the higher affinity receptors that aid the release of GABA and dopamine (Kirch DG., Gerhardt GA., Shelton RC., *et al*, 1987) giving the anxiety reduction and mood elevation that most smokers report (Jarvik ME. & Schneider NG., 1992). Therefore schizophrenic smokers, who tend to smoke more heavily (see section 2.4.4), may be targeting the defective lower affinity alpha-7 receptor which has also been shown to be present in decreased numbers in the hippocampi of schizophrenic patients. (Freedman R., Hall M., Adler LE., *et al*, 1995)

The P50 attentional mechanism is not the only information-processing domain that is abnormal in schizophrenia. Smooth pursuit eye movements (SPEM) have also been documented as aberrant in this population (Levy DL., Holzman PS., Matthysse S., *et al*, 1994). A number of studies have reported that nicotine administration to schizophrenics, by smoking cigarettes (Klein C. & Andresen B., 1991) (Olincy A., Ross RG., Young DA., *et al*, 1998), improves SPEM performance. Furthermore improvements due to nicotine consumption in other areas of cognition have also been shown including in the Continuous Performance Task (CPT), a systematic measure of cognitive deficits in patients (Levin ED., Wilson W., Rose JE., *et al*, 1996) as well as in reducing antisaccade errors in task impaired schizophrenic subjects (Larrison-Faucher AL., Matorin AA. & Sereno AB., 2004). In the latter study it was noted however that not all the ill subjects showed the antisaccade deficit but those that did tended to have a higher daily consumption of cigarettes. Again such findings would give credence to the idea that schizophrenic patients are more likely to smoke, as per the results of the meta-analysis and smoke more heavily (as was suggested in the results of hypothesis 3), to self-medicate for such abnormalities.

The finding from hypothesis 7, that there is a clear trend for those at a higher risk of developing schizophrenia to be more likely to be ever smokers compared to the well controls, also correlates with what is known about the heritability of the P50 gating deficit (Waldo MC., Carey G., Myles-Worsley M., *et al*, 1991) as well as other attentional endophenotypes including the decreased P300 amplitude (Blackwood DH., St Clair DM., Muir WJ., *et al*, 1991) and abnormal SPEM (Holzman PS.,

Kringlen E., Matthysse S., *et al*, 1988). These problems are found in about 50 percent of the first degree relatives of the schizophrenic patients studied following an autosomal dominant pattern of inheritance. This suggests that the presence of, for example, the P50 gating deficit is not enough in itself to lead to the development of the full schizophrenic constellation of symptoms (Leonard S., Adams C., Breese CR., *et al*, 1996). A study of siblings discordant for schizophrenia and the P50 deficit was undertaken (Waldo MC., Cawthra E., Adler LE., *et al*, 1994) which showed that those who were ill had the P50 defect as well as a reduction in the volume of the hippocampus. Those who had the gating deficiency but a normal hippocampal volume were not affected meaning that expressed alone, neither abnormality was sufficient for disease development. This finding in first degree non-smoking relatives of schizophrenic probands, who were free of the possible confounding effects of neuroleptic and anticholinergic mechanisms, was also established by Adler *et al.* who showed that nicotine chewing gum could evoke the inhibitory mechanisms for the P50 system which were faulty in them (Adler LE., Hoffer LD., Griffith J., *et al*, 1992).

From the above therefore it may be that those from the EHRS who are at high-risk of developing schizophrenia and are smokers may well have the P50 gating deficit genotype, or other attentional endophenotype abnormality, and are treating themselves accordingly. Of these subjects it is possible that those who go on to become ill are unable to fully treat this deficit due to the lack of protective function afforded to them from a small hippocampus but they have a higher prevalence rate of being ever smokers as they must ‘work harder’ to overcome this. The group of those who are at high-risk with no psychotic symptoms may have a higher prevalence rate than the well controls as they are merely trying to self-medicate for the P50 deficit. The high-risk group with some psychotic symptoms but not the full syndrome of schizophrenia lie somewhere in-between these two phenotypes, and possibly genotypes, which reflects the complexity of this disorder.

The final part of the P50 puzzle is the finding that clozapine normalises this gating deficit in those who respond to this medication as measured by an improvement in

their Brief Psychiatric Rating Scale (BPRS) (Overall JE. & Gorham DR., 1962) scores by 20 percent from when they were taking typical antipsychotic treatments (Nagamoto HT., Adler LE., Hea RA., *et al*, 1996). Further evidence for clozapine's possible interaction with nicotinic systems is found in a study showing that schizophrenic patients actually decrease their cigarette smoking during clozapine treatment (McEvoy JP., Rose JE., Levin ED., *et al*, 1994) a finding that was added to by Procyshyn et al. who demonstrated that those patients who were on clozapine had lower expired carbon monoxide values as well as lower self-reported levels of smoking (Procyshyn RM., Ihsan N. & Thompson D., 2001). These results may suggest a strong cholinergic influence on the efficacy of antipsychotics as well as in the pathogenesis of schizophrenia but they must be tempered with the consideration that patients on typical neuroleptics may be smoking more cigarettes to self-medicate for these drugs' side-effects as the author will discuss below.

SECTION 5.2.3 Schizophrenic Patients Are Smoking Cigarettes to Help Relieve the Negative Symptoms of Schizophrenia

It has been asserted in recent years that neurobiological factors provide the strongest explanation for the connection between smoking and schizophrenia as direct neurochemical interactions can be investigated and demonstrated (Lyon ER., 1999). One such factor is that proposed by Dalack et al. (Dalack GW., 1998) who consider that cigarette smoking by schizophrenics may be an attempt to treat the negative symptoms of their illness including anhedonia, amotivation, social withdrawal and apathy which are present due to dysfunctions within the mesolimbic reward circuitry. Because of nicotine's complex effects on the central dopaminergic system it might provide a way to activate this abnormal reinforcement / reward system (Combs DR., 2000).

The basis for this idea is that schizophrenia has been considered to be a disease caused by a hyper-dopaminergic state (see section 1.2.2) and as such, treatments, especially the typical neuroleptics, have been geared towards their dopamine receptor

blocking potential. Despite their relative success in treating the positive symptoms of schizophrenia, such as delusions and hallucinations, they have been less effective at remedying the negative symptoms (Johnstone EC., Crow TJ., Frith CD., *et al*, 1978) as these may be due to a reduction in dopaminergic transmission. This may be why other psychotropic chemicals, including amphetamines, have been shown to alleviate negative symptoms as they increase dopamine activity within the brain (Van Kammen DP. & Boronow JJ., 1988) and, indeed, such stimulants with dopaminergic properties are preferentially used by patients with schizophrenia (Patkar AA., Alexander RC., Lundy A., *et al*, 1999). Interestingly nicotine has also been shown in preclinical studies to be a promoter of dopamine release in the mesolimbic system (Imperato A., Mulas A. & DiChiara G., 1986) which has been suggested to be because it increases the release of dopamine with its action on presynaptic terminals (Svensonn T. & Enberg G., 1980). Tobacco smoke has also been shown to reduce the central activity of the monoamine-B (MAO-B) enzyme by up to 40% which would also lower the degradation of dopamine hence increasing nicotine's pro-dopaminergic activity (Fowler JS., Volkow ND., Wang G-J., *et al*, 1996).

In conjunction with the above data nicotine has also been shown to induce a dose-dependent increase in neuronal activity in some brain regions including the nucleus accumbens, amygdala, cingulate and frontal lobes (Stein EA., Pankiewicz J., Harsch HH., *et al*, 1998). This has relevance to the high prevalence rate of cigarette smoking in the schizophrenic population bearing in mind that schizophrenic patients display hypofrontality which has been reported to be associated with the negative symptoms of schizophrenia (Svensson TH., Grenhoff J. & Enberg G., 1990; Weinberger DR., 1987). The latter study in rats found that nicotine produced a significant partial reversal of the dysfunction of mesolimbocortical dopamine cells which had been induced by cold inactivation. It has been suggested that smoking may therefore represent an attempt to self-medicate the impaired influence of the frontal/prefrontal cortex on the mesolimbocortical dopamine systems of schizophrenics which may be part of the explanation for the high prevalence rates found in the systematic review completed for this thesis.

Other clinical studies (Hall RG., Duhamel M., McClanahan R., *et al*, 1995), but not all (Herran A., Santiago A., Sandoya M., *et al*, 2000), have also demonstrated a link between negative symptoms and tobacco use. One such study found a positive association between severity of smoking, negative symptoms and other symptoms reflecting impairments in attention, orientation and thinking irrespective of possible confounders including medication dose and with no relationship found to positive symptoms (Patkar AA., Gopalakrishnan R., Lundy A., *et al*, 2002). The authors of this study raise the question of the line of causality between cigarette smoking and symptomatology, a problem that is evident throughout the papers examined for this thesis; they suggest that there are two alternative explanations for the association. The first is that patients are indeed self-medicating which would integrate well with what has already been detailed in this section regarding the neurobiology of schizophrenia as well as what patients subjectively report (Glassman AH., 1993). The second implies the reverse in that nicotine use worsens the clinical picture by exacerbating negative symptoms by desensitising nicotinic receptors therefore reducing cholinergic activity in the prefrontal cortex (Vezina P., Blanc Glowinsk J. & Tassin J., 1992).

In addition to what has already been described in this section is the finding that tobacco addiction has been linked to an earlier age of onset in schizophrenia (Sandyk R. & Kay SR., 1991) which, in turn, has been found to have a significant association with the presence of negative symptoms (Johnstone EC., Owens DGC., Bydder GM., *et al*, 1989). Sandyk *et al.* suggest this association, which is due to an alteration in the function of the brain's reward circuitry notably within the ventral tegmental area, is because of decreased dopamine activity in the mesolimbic system as a whole and therefore leads to compensatory excessive nicotine intake and ultimately addiction. In terms of the applicability of this to the EHRS sample, a recent study (Owens DGC., Miller P., Lawrie SM., *et al*, 2005) showed that those in the high-risk group who developed the full schizophrenic illness at the last assessment had a significantly worse rating in their negative symptom score from the PSE in comparison to those at high risk who remained well and by a greater amount than the well control group. This correlates with the data presented from the same sample in that the HR-ill group

show a trend of having more ever-smokers by the final assessment than either of the other two aforementioned groups. So it may be that those at high-risk are already self-medicating for their deficit. Unfortunately this potential answer is confounded however by the findings from Owens et al. that positive symptomatology followed the same pattern.

All of the above has implications for what is known about the treatment of schizophrenia. Clozapine has been shown to reduce smoking rates in schizophrenic patients (Procysbyn RM., Ihsan N. & Thompson D., 2001) as well as having superior efficacy in treating negative symptoms and clearing hypofrontality (Shafari M., 2005). It is not unreasonable to consider that the three effects are linked and that clozapine may prove an effective treatment for nicotine dependence in schizophrenia and provide clues to the aetiology of the condition.

SECTION 5.2.4 Cigarettes Are Being Used by the Schizophrenic Population to Treat Their Positive Symptomatology

A third explanation for the high prevalence rate shown for cigarette smoking in the schizophrenic populations studied (see section 2.3.6) as well as the significant odds ratio established by the meta-analysis conducted (see section 3.4.2) is that patients are treating their positive psychotic symptomatology with nicotine.

The above may seem counter-intuitive however in light of what has been noted in the introductory sections of the thesis concerning how cigarettes affect smokers' brains (see section 1.4.3) and the role of positive reinforcement in maintaining dependence (see section 1.5.4). This is particularly in relation to the effect that nicotine has in elevating extracellular levels of dopamine in the brain (Nissel M., Nomikos GG. & Svensson TH., 1994; Watkins S., Koob GF. & Markou A., 2000) when positive symptoms appear to be associated with a hyperdopaminergic state (Weinberger DR., 1987). If this is true then what is the explanation for so many schizophrenics smoking so much? One author feels that any negative impact on positive symptomatology may be outweighed by the potential relief that cigarettes give to

negative symptoms (Forchuk C., Norman R., Malla A., *et al*, 1997) a subject that I elaborated on in the previous section. A neurobiological explanation may be possible as it has been demonstrated, in animal models, that chronic administration of nicotine leads to a desensitisation of central nicotine receptors and an overall decrease in dopamine release (Grenhoff J., Jansson AM., Svensson TH., *et al*, 1991; Kirch DG., Gerhardt GA., Shelton RC., *et al*, 1987; Lapin EP., Maker HS., Sershen H., *et al*, 1989). These results have not been uniformly replicated as others have shown an increase in dopamine with chronic nicotine administration (Fung YK., 1988) and still others have demonstrated no change to dopamine levels (Lapin EP., Maker HS., Sershen H., *et al*, 1987). This makes the interpretation of such results and their link with a possible self-medication effect of nicotine on positive symptoms difficult at this time. It would be of interest though to examine how with chronic use of cigarettes the patient's symptoms, both positive and negative, changed with time. As evidence for the potential interaction between the cholinergic and dopaminergic systems a model has been put forward about how they might interact to affect positive psychotic symptomatology. The proposers of this (Procyshyn RM., Patel K. & Thompson DL., 2004) noted that significantly more smokers were prescribed an anticholinergic agent than non-smokers and that the administration of such centrally acting agents results in unopposed nicotinic cholinergic receptor agonism by endogenous acetylcholine thus giving an amplification of positive symptoms secondary to increased dopaminergic activity. This increase is then attenuated by the desensitisation of nicotinic receptors described above.

Clinical studies have also been performed in this field with the assumption that if self-medication is occurring then there should be a correlation between cigarette consumption and symptomatology. Goff *et al*. reported that smokers had a higher BPRS score for both positive and negative symptoms (Goff DC., 1992) while another study (Ziedonis DM., Kosten TR., Glazer WM., *et al*, 1994) found that smokers had more positive symptoms than non-smokers with the heaviest smokers having the highest levels of positive symptoms. These were both cross-sectional studies which limits the possibility of establishing a line of causality between the two factors so it may be that smoking is a marker of a patient trying to manage a worse

illness or it may be that cigarette smoking may worsen positive symptoms. This problem has been addressed in three case series, the first of which (Dalack GW., 1996) noted that three subjects, albeit retrospectively, reported worsening of positive symptoms with cessation of smoking. Secondly Lawn et al. (Lawn SJ., Pols RG. & Barber JG., 2002) describe how smoking was perceived by more than half of the patients they studied to play a role in alleviating the positive symptoms of schizophrenia with a poignant description by one of their patients:

“And at the moment there doesn’t seem to be any better solution to stopping the negative [psychotic] thoughts than smoking”.

The third (Hamera E., Schneider JK. & Deviney S., 1995) showed that there was an exacerbation of prodromal symptoms associated with less nicotine use. This last study has relevance to the results from the Edinburgh High-Risk study, presented in section 4.5.3, as it may explain why there is evidence of a trend for a higher prevalence rate of being an ever-smoker in those at high-risk of developing schizophrenia even when they have not gone on to develop the illness as yet. It is possible that the prodromal symptoms are already being managed in this group by cigarette smoking.

The final finding which further corroborates the idea of self-medication for such symptoms is that a diagnosis of the paranoid subtype of schizophrenia significantly correlated with cigarette smoking whereas the other subtypes did not (Combs DR., 2000). This subtype has a greater burden of positive symptomatology than the other subtypes and one answer to this could be that the increased smoking rates reflect this groups’ attempt to attenuate their paranoid symptoms. This is not the only possible explanation as dysphoria is particularly associated with positive symptoms of schizophrenia (Lysaker PH., Bell MD., Bioty SM., *et al*, 1995) and nicotine use may reflect an attempt to treat this affective abnormality due to cigarette’s potential euphoriant effects (Pomerleau OF. & Pomerleau CS., 1992).

SECTION 5.2.5 Antipsychotic Side-effects Can Possibly Be Helped by Smoking Cigarettes

The antipsychotic drugs that are consistently used to treat schizophrenia have a number of unpleasant side effects, even in the normal population, where it can be seen that a single 5mg dose of oral haloperidol leads to a significant increase in nicotine intake (Dawe S., 1995). This suggests that there may well be a link between what medication is used and how much people smoke. It has been hypothesised that cigarettes may serve to reduce the side effects of antipsychotic treatments in two ways which may be a large incentive for patients to start or continue smoking.

The first of these is that cigarettes have a pharmacokinetic interaction with neuroleptic treatment (Goff DC., 1992). This is not a nicotine specific effect but is as result of polycyclic hydrocarbons in cigarette smoke stimulating the hepatic microsomal system which induces enzymes to increase the metabolism of psychotropic medications (Ziedonis DM. & George TP., 1997). The putative enzyme is within the cytochrome P450 group, known to be involved in the oxidative metabolism of the majority of antipsychotics (Lyon ER., 1999), and has been suggested to be the 1A2 isoform (Nemeroff CB., DeVane CL. & Pollock BG., 1996). A number of studies have demonstrated an association between the clearance of haloperidol, as well as a reduction in it and its reduced form's level in the bloodstream, with cigarette smoking (Jann M., Saklad SR., Ereshefsky L., *et al*, 1986) (Miller DD., Kelly MW., Perry PJ., *et al*, 1990). This corroborates with other work that has shown that this reduced level then requires an increase in dosage to attain therapeutic levels of neuroleptics, for example the mean chlorpromazine equivalent in smokers is 590mg compared to 375mg for non-smokers (Ziedonis DM., Kosten TR., Glazer WM., *et al*, 1994). Other studies have reported a similar finding with smokers consistently prescribed a higher dosage of antipsychotics than non-smokers (Glassman AH., 1993; Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986).

These findings though do not answer the question as to why the association persists. Is it due to the patient treating the side effects from their higher dosage of medication or are psychiatrists prescribing more medication to their schizophrenic smokers to try and counter the pharmacokinetic effects of cigarette consumption? One answer to this question may be found in work that has investigated the connection between specific antipsychotics and smoking behaviour. It has been noted that patients treated with haloperidol smoked more heavily, as measured by expired carbon monoxide measures, plasma nicotine and cotinine levels, than when they were drug free (McEvoy JP., Freudenreich O., McGee M., *et al*, 1995). The same group, and others (Procyshyn RM., Ihsan N. & Thompson D., 2001), have shown that clozapine users have lower prevalence rates of smoking which has been hypothesised to be due to the atypical agents elevating levels of cortical dopamine in a manner similar to nicotine (Moghaddam B. & Bunney BS., 1990). The older typical drugs effectively antagonise the central dopaminergic system meaning that this system could be being alternatively self-managed by the smoking schizophrenic as well as them reducing the actual blood levels of medication which would lead to less side effects (Lyon ER., 1999). This latter idea was considered in a study which demonstrated that smokers had lower levels of chlorpromazine-induced sedation than non-smokers, a finding that was attributed to lower plasma chlorpromazine concentrations (Swett CJ., 1974) in the smoking group due to their presumed activation of the hepatic microsomal enzyme system.

Further to the above there is the second way that cigarettes may help schizophrenics manage medication related problems in the light of what is known about how nicotine exerts its effects on the dopaminergic function of the CNS and how this could influence the development and presentation of neuroleptic induced extrapyramidal movement disorders including parkinsonism and tardive dyskinesia (TD) (Lohr JB. & Flynn K., 1992).

There are a number of reasons to consider a relationship between nicotine, dopamine and the dyskinesias. The first of which is the speculation that smoking may have a protective effect against the development of idiopathic Parkinson's disease, which is

known to involve a loss of dopaminergic neurons in the substantia nigra leading to a net dopamine deficit, as has been suggested by a number of cross-sectional studies. One of these, Kessler *et al.*, has shown that Parkinson's disease is less likely to occur in smokers (Kessler II. & Diamond DL., 1971) and this may be due to nicotine's agonist effect on the striatal dopamine system (Morens DM., Grandinetti A., Reed D., *et al.*, 1995). A second reason for a possible interdependence between smoking and parkinsonism is that monozygotic twin studies have consistently shown that in Parkinson's disease environmental factors outweigh genetic ones in its aetiology with affected co-twins being significantly less likely to be smokers than their unaffected siblings (Bharucha NE., Stokes L., Schoenberg BS., *et al.*, 1986). In the light of such ideas it is not surprising to find that studies in this area have demonstrated that measures of neuroleptic-induced parkinsonism were lower in smokers than in non-smokers (Decina P., Caracci G., Sandyk R., *et al.*, 1990) (Goff DC., 1992; Sandyk R., 1993). The last of these studies (Goff DC., 1992) showed that this effect was highly significant and appeared to be independent of gender, age and anticholinergic prescription with the number of cigarettes smoked daily having a significant correlation with parkinsonism ratings. Again the question arises of whether or not patients smoke in response to extrapyramidal side-effects or whether the protective antiparkinsonian effect, as seen in the normal population, is at work. Goff *et al.* address this by stating that the smokers in their group started the habit on average 8 years before starting on neuroleptic treatment which would favour the latter explanation.

Interestingly these findings in favour of smoking are in contrast to what has been seen in animal studies where smoking worsens extrapyramidal symptoms acutely as it induces catalepsy in mice (Baumann RJ., Jameson HD., McKean HE., *et al.*, 1980) however with chronic administration of nicotine there is a protective effect against induced degeneration of nigrostriatal neurons (Janson AM., Agnati LF., Fuxe K., *et al.*, 1988) which is an animal model for parkinsonism. This chronic ameliorating effect may be due to nicotine decreasing the vulnerability of nigrostriatal neurons by desensitising excitatory nicotinic receptors leading to reduced firing rates and lower energy demands on the neurons (Fuxe K., Janson AM., Jansson A., *et al.*, 1990). In

addition it may be that after chronic nicotine administration the brain's levels of acetylcholine are reduced (Balfour DJK., 1984). With the knowledge of all these actions that nicotine has on reducing the unpleasant side-effects of antipsychotic treatment it seems hardly surprising that there is such a high prevalence rate of smoking found in the systematic review and that the odds ratio within the meta-analysis showed a significant association between smoking and schizophrenia. Schizophrenic patients, when they start smoking, do so often prior to being treated with neuroleptics, as has been noted above as would be the case in the high-risk group at the first assessment point of the EHRS. Hence medication may not be the initiator of the habit but would certainly seem to be a factor in the continuing persistence, and perhaps heaviness, of smoking when patients do start treatment with psychotropic medications.

As has been outlined there are strong links between nicotine and dopamine which has led researchers to consider the interrelationship between cigarette smoking and tardive dyskinesia (TD) also. TD is characterised by involuntary movements of the orolingual, facial, truncal and extremity regions. Its incidence increases with duration of neuroleptic exposure and this has been hypothesised to be due to dopamine receptor supersensitivity which arises from chronic receptor blockade by antipsychotics (Lohr JB. & Flynn K., 1992; Ziedonis DM. & George TP., 1997). As the author has outlined previously nicotine administration may lead to dopamine release and as such it would be expected that smoking would therefore exacerbate TD or promote its emergence though studies conducted in this area have yielded differing results. Yassa et al. (Yassa R., Samarthji L., Korpassy A., *et al*, 1987) showed a significantly higher prevalence of TD in smokers compared to non-smokers though they were on higher doses of neuroleptics presumably as a result of smoking's effect on microsomal enzymes but Menza et al. (Menza MA., Grossman N., Van Horn M., *et al*, 1991) found that there was no difference between smokers in terms of the severity or frequency of TD. The latter study's result fits with an alternative theory that has been suggested for the dopamine-nicotine interaction which is that chronic nicotine intake could reduce the risk of TD by blocking an increase in dopamine receptor density as has been demonstrated in a pre-clinical

study (Prasad C., Spahn SA. & Hiromasa I., 1989). This finding has been replicated, albeit in a case-control study of 1 smoker versus 1 non-smoker both of whom had been treated with haloperidol for some years, which showed that D2-dopamine receptor upregulation had not occurred in the smoker suggesting a protective effect of smoking on TD (Silvestri S., Negrete JC., Seeman MV., *et al*, 2004).

The potential impact on the prevalence data within this thesis is that smoking, if it worsens TD, would intuitively mean that patients with schizophrenia would smoke less and vice versa. However, if the patient is already addicted to smoking and it's potential beneficial effects, for example on negative and positive symptoms, outweigh the negative effect of developing tardive dyskinesia then it may be that the cost of giving up is greater than the cost of continuing. This is an area which highlights the need for a comprehensive cohort study looking at smoking behaviours and their interaction with all of the problems associated with schizophrenia to establish how they are temporally related.

SECTION 5.2.6 Because The High-Risk Patients and Those with Schizophrenia Possess a Shared Vulnerability to Being Both Schizophrenic and Cigarette smokers

As has been outlined in the above sections there has been a distinct lack of studies examining the temporal relationship between tobacco smoking and schizophrenia. Other diagnoses have had a greater exposure to this form of investigation most notably depression. Kendler et al. in the results of a twin study (Kendler KS., Neale MC., MacLean CJ., *et al*, 1993) theorised that genetic vulnerability could explain why depressed patients smoke approximately twice as much as the well population (Glassman AH., 1993). From this thesis it is apparent that the prevalence rate of cigarette smoking in the schizophrenic population is higher even than this.

With the above in mind, as well as with the facts surrounding the heritability of the P50 gating (Adler LE., Hoffer LD., Griffith J., *et al*, 1992) and other attentional

deficits (Blackwood DH., St Clair DM., Muir WJ., *et al*, 1991), and with the knowledge that genetic linkage studies have supported a role for the alpha-7 nAChR within these faulty mechanisms in schizophrenia, as well as what was described in section 1.5.2 regarding the heritability of smoking in the normal population, it is not unreasonable to speculate that this high rate of cigarette consumption in schizophrenia may also be partly explained by genetic factors. Furthermore, work surrounding candidate gene investigations has identified putative genes such as the D2/D3/D4-dopamine receptor genes to be involved with the pathogenesis of schizophrenia and also with cigarette smoking (Yoshimasu K. & Kiyohara C., 2003).

Following from this it has been noted that 50 percent of patients had started daily cigarette smoking prior to the onset of their first schizophrenic episode (De Leon J., 1996). This result has been further confirmed in a number of other studies which showed a range of proportions (49-90 percent, mean 77%) for those who started smoking before the onset of their illness (Gurpuegui M., Martinez-Ortega JM., Aguilar MC., *et al*, 2005) (Campo-Arias A., Haydar-Ghidays R., Bermusdez-de-Leon A., *et al*, 1998) (De Leon J., Diaz FJ., Rogers T., *et al*, 2002) (Uzun O., Cansever A., Basoglu C., *et al*, 2003) (Liao D-H., Yang J-Y., Lee S-M., *et al*, 2002) (Beratis S., Katrivanou A. & Gourzis P., 2001) (Kelly C. & McRreadie RG., 1999). In one of these the mean smoking onset age preceded schizophrenia by 11 years (Kelly C. & McRreadie RG., 1999). There is some debate in the literature as to whether this early initiation of smoking should be regarded as a symptomatological part of the prodrome of the illness (Riala K., Hakko H., Isohanni M., *et al*, 2005) or as an independent risk factor for schizophrenia itself (De Leon J. & Diaz FJ., 2005). If the latter view is considered then it would seem that those who are going to go on and develop schizophrenia may have some factor that makes them more vulnerable to start smoking. Such a factor may be genetic in nature as unaffected co-twins of schizophrenic probands have been shown (Lyons MJ., Kremen WS., Eisen SA., *et al*, 2002) to have a high rate of ever smoking close (83%) to that of their affected co-twins (86%). This would be in keeping with what I have suggested about how individual's genotypes influence whether they smoke or not particularly in terms of

sensory and information processing abnormalities that are present throughout affected families.

The alternative view of smoking as a symptom of the prodrome of the illness corresponds more with what has already been written above about how smoking may be used as a form of self-medication by patients. Both points of view require further investigation to take into consideration how genetic factors may influence vulnerability to start smoking or develop schizophrenia. One such investigation is found within this thesis.

From the EHRS section it is apparent that there was a trend ($p=0.09$) for those who were at high risk of developing schizophrenia and had psychotic symptoms (HR+) at the first assessment point when compared with the group who were at high risk without psychotic symptoms (HR-). The crude unadjusted odds ratio for this data showed a result of 2.3725 (95% confidence intervals of 0.9 to 6.5). This would seem to correlate more with the self-medication argument in that the symptomatic group may be treating their prodromal symptoms whereas those who had no symptoms, but had the genetic vulnerability for schizophrenia, were no more likely to be ever smokers than the control group ($p=0.69$).

In conjunction with these findings is that those who were at high-risk of developing schizophrenia and then went on to do so by the fourth timepoint had a near trend level ($p=0.11$) increase in their rate of ever smokers compared to those from the HR group who did not become unwell ($p=0.07$ when analysed alone with the ill group alone which indicates a statistical trend) or the control group. This may be because of an underlying additional vulnerability, beyond having a higher genetic risk, within the HR group who became ill that was not shared with the high-risk group who did not develop any or all of the full syndrome of schizophrenia. Alternatively it may again be that there is an underlying neurophysiological deficit that is being treated by those who become unwell at the first time point such as the P50 gating deficit.

As such, further investigation is required into this finding as it is possible that smoking may be a provocative factor for developing schizophrenia in the high-risk population as has been suggested by some who consider that repeated activation of the mesolimbic dopaminergic system over a long period by nicotine may precipitate the onset of schizophrenia in vulnerable individuals rather than reflecting an underlying shared vulnerability for nicotine dependence (Kelly C. & McReadie RG., 1999). This hypothesis seems unlikely given the evidence for desensitisation of the dopaminergic system over time (Pidoplichko VI., DeBias M., Williams JT., *et al*, 1997) though intermittent smoking or relapse of dependence after abstinence might worsen positive psychotic symptoms (Chong SA. & Choo HL., 1996; Foulds J. & Toone B., 1995). Therefore useful extensions of the work contained in this thesis would be to correlate symptomatology with smoking prevalence and to measure P50 potentials and other attentional endophenotypes serially within high-risk populations. Other work could focus on neuroimaging to establish whether the development of schizophrenia correlated with cigarette smoking and another factor together such as hippocampal volume as was suggested earlier (Waldo MC., Cawthra E., Adler LE., *et al*, 1994).

SECTION 5.3.1 But Maybe It's Not All Biological

Beyond the biological reasons for why those with schizophrenia and those at a higher risk for developing the illness might be more likely to be smokers are the ideas that have been put forward regarding how psychological and social factors might affect these prevalence rates.

From this thesis it was apparent that there was a non-significant difference between the prevalence rates for smoking in inpatient and outpatient settings, which was postulated with hypothesis 1, but despite this finding some authors have suggested that there is a role played by institutions in maintaining smoking habits in the psychiatrically unwell. Masterson *et al*. suggest that 'smoking is an important component of institutional life, cigarettes being widely used by the nursing staff as a

form of token economy' (Masterson E. & O'Shea B., 1984) whilst another study found that a high percentage of psychiatric staff smoked and, more worryingly, almost a quarter of these staff denied that there were hazards in smoking (Mester RE., Toren P., Ben-Moshe Y., *et al*, 1993). This latter study also reported that a third of patients were aware that smoking by the staff encouraged them to do so, a fact that the employees were unaware of. Alongside this is what has been written in the section about cessation and treatment options (section 1.6.5) regarding the low percentage of patients who are counselled about smoking by psychiatric staff (Himelhoch S. & Daumit G., 2003) (Lawrie SM., Buckley LA., Ulyatt BC., *et al*, 1995) which suggests that though patients may initiate smoking prior to hospitalisation, as has been stated earlier, those in the psychiatric profession and paramedical services may be doing little to reduce the prevalence of cigarette smoking once there is contact with them.

The effect of institutionalisation has been refuted by others who note that the prevalence of smoking is raised in both in- and outpatient settings (Hughes JR., Hatsukami DK., Mitchell JE., *et al*, 1986) as I have shown also. De Leon *et al*. note that non-schizophrenic psychiatric inpatients have a higher rate of smoking than the general population from which they come but not to the level shown in schizophrenia and thus discard institutionalisation as a factor (De Leon J., Dadvand M., Canuso C., *et al*, 1995). Further work from this group (De Leon., 2002) also suggests that long hospitalisation may even decrease smoking. In reply to this argument it has been suggested that institutionalisation may affect schizophrenics differentially from non-schizophrenics as the former may be anxious in response to being institutionalised and the latter may not be (Smith GL., 1996). As far as this debate's relevance to those in the EHRS is concerned it is limited as those who were at high-risk and went on to develop the illness were already smoking more at the first assessment point prior to them becoming unwell and thus hospitalised.

Further psychosocial interpretations of the elevated cigarette smoking rates in schizophrenia have been propounded including the 'Psychological Tool Model', the role of patient's demographic and educational characteristics as well as the impact of

personality all of which have all been dealt with in section 1.5.6. As an addendum to these potential elevators of the prevalence rate is the role of gender in the results of hypotheses 4 and 6 which demonstrated that males were more likely to be smokers and to smoke more heavily than female smokers. As stated in these sections this is in keeping with what is known about patterns of smoking within the well population. It has however been suggested that the better pre- and post-morbid functioning of female schizophrenics may protect them from the need to smoke (Beratis S., Katrivanou A. & Gourzis P., 2001).

The final psychological aspect for the smoking rate to be elevated in the schizophrenic population is the subjective reasons provided by the ill for their habit. There have been few studies in this area but those that have been published report that schizophrenic patients smoke for much the same reasons as those who are not schizophrenic - primarily 'relaxation' (80%), 'habit' (67%) and 'calming nerves' (52%) - with nearly a quarter concurring, without knowing it, with the self-medication hypothesis and identifying psychiatric issues as influencing their smoking behaviour (Glynn SM. & Sussman S., 1990). A later study demonstrated that those with mental illness smoked in line with 4 major themes namely 'habit and routine' (58%), 'socialisation' (58%), 'relaxation' (42%) and 'nicotine addiction' (33%) (Van Dongen CJ., 1999) though this latter percentage may represent denial.

Despite these varied psychological theories, which could as well be applied to the well population, it is hard not to think that the biological correlates I have discussed in this thesis might not be more applicable to the strong association between schizophrenia and cigarette smoking that has been demonstrated throughout.

SECTION 6

CONCLUSION

There has been a consistent theme in the results that the author have reported throughout this thesis which has been that cigarette smoking and schizophrenia are inextricably linked. The author has shown a clear and consistent association both in the systematic review and the meta-analysis that those who have schizophrenia are far more likely to smoke than those in the general population regardless of gender, setting or country. Furthermore it has been demonstrated, from the Edinburgh High-Risk Study, results that show that those who have a genetic predisposition to becoming schizophrenic are already smoking more than their well and high-risk counterparts who stay well when they were first assessed for this study. So why is this? The answer seems to lie primarily in the neurobiology and neurophysiology of the illness.

The presence of hard-wired information processing deficits in those who are schizophrenic and their first-degree relatives suggest that these groups are at a disadvantage when presented with the complex stimuli we find around us in the world. The author would suggest that these abnormalities may lie behind some of the characteristic symptoms we see in the disorder most probably in the domain of the perceptual disturbances that are almost its hallmark. This is because problems with managing incoming auditory data, in the case of the P50 deficit, and visual information, as with difficulties in tackling smooth-pursuit eye movement tasks, could lead to a lower threshold for the misinterpretation of such stimuli and hence auditory and visual hallucinations. Though these deficits alone are not enough to explain why schizophrenic patients are so much more likely to smoke cigarettes as their relatives with the same deficit do not manifest the same symptoms. As has been discussed in the sections dealing with information processing it seems to be the requirement of another abnormal factor to lead to the symptomatology being manifested such as a reduction in hippocampal volume that may lead to the full

syndrome of schizophrenia. Alternatively it may be that the processing problems tip the balance unfavourably towards psychosis and without smoking cigarettes the symptoms may be much worse or it may be that those who were at high-risk and do not become unwell are managing to keep the bar raised high enough for information to be handled in a normal fashion.

This tendency for there to be the association described herein between positive symptoms of schizophrenia and cigarette smoking is difficult to interpret. There remains the continuing chicken and egg question in respect to both these symptoms and negative symptoms as they interact with the self-medication hypothesis. Elevated levels of positive symptoms are associated with elevated rates of smoking but is it because nicotine is having an agonist effect on the mesolimbic-mesocortical dopaminergic system or is it that positive symptoms, such as hallucinations, are being treated by the patients themselves with cigarettes which are causing a desensitisation of nicotinic receptors and hence a reduction in the activity of the dopaminergic system? This question requires more emphasis to be placed on prospective studies being carried out by researchers however studies such as the EHRS do afford the prospect of solving this puzzle as by studying the association of selected symptom profiles to cigarette smoking rates then it may become more obvious what leads to what.

This problem with establishing the line of causality also presents itself when considering what the impact of negative symptoms are on cigarette smoking behaviours or vice versa. It would seem intuitively true that if patients are socially isolated, amotivational and dysphoric they would tend to sit for longer periods in hospital smoking rooms where company is at least more available. But when the evidence for the faulty reward system present in schizophrenia is considered, as well as the increasing knowledge of the role hypofrontality plays in the deficit state associated with this condition, it can seem even more intuitive that patients may be trying to counter these dysfunctional neural circuits by activating them with nicotine and its manifold secondary neurochemical effects. The complexity continues though as if the idea that patients are activating their brains with nicotine is true then are

they not placing themselves at more risk of worsening their psychotic symptoms? It would seem that neuroimaging methods, especially functional techniques, may provide a clearer explanation of this as it may be that the systems which underlie the pathogenesis of positive and negative symptoms are being differentially activated by cigarette smoking in schizophrenics and that there may be some or no trade-off between them.

Finally on the neurobiological theme there is the suggestion that there is a shared vulnerability for tobacco dependence and schizophrenia. This seems to underpin much of what is known about the P50 deficits and other attentional endophenotypes that are found in schizophrenia and provides a plausible explanation for how the two disorders might be intertwined. If schizophrenia is a disorder that affects circuits in the brain that are linked to reward, information processing and motivation then it does not seem unreasonable for it to lead to problems with dependence on substances which also are linked to these areas.

The illness itself is not the only explanation for why people with schizophrenia smoke though because it may be partly an iatrogenic effect. The side-effects of the medications that are primarily used to treat schizophrenia, namely neuroleptics, are no doubt a heavy burden for patients. The link between parkinsonism and cigarette smoking seems to suggest that nicotine may provide a helpful role in alleviating this problem but it does not explain why those in the EHRS who were smoking more at the first assessment point were doing so. In this case, as with the effects of institutionalisation, it cannot be the only explanation for why there is such a high prevalence rate as neither medication nor hospitalisation were part of the equation at the subjects' first meeting with the interviewers. The author would suggest that it is the neurobiological substrates and symptoms that lead to the elevated initiation of cigarette smoking in schizophrenia and to some extent its persistence but when other non-schizophrenic groups might think of quitting those who have become unwell now have additional reasons to continue smoking such as medication, boredom or indeed worsening of symptoms with abstinence. Again, prospective studies may give the field of psychiatry a better understanding of how the processes are linked.

Whatever the reason for the association it still leaves the profession with the task of managing patients' physical health which includes enabling them to stop smoking. Government initiatives are becoming increasingly preoccupied with getting the population to stop smoking also. If we and our patients are aware of the damage smoking is doing to their bodies then there must be a greater emphasis on smoking cessation which has been shown to be effective in psychiatric populations. However if nicotine is a potential therapeutic agent in schizophrenia, for all the possible reasons stated previously, then greater emphasis should be placed on finding a non-carcinogenic alternative to cigarettes and then to provide it to patients.

The final question that is raised by the consideration of nicotine as a potential weapon in the psychiatrist's armamentarium is whether it may be appropriate for there to be a re-evaluation of the dopamine hypothesis of schizophrenia to increase its level of complexity to not only include serotonin, GABA and glutamate but also nicotine. The author has reported on many pre-clinical and clinical studies which show a clear line of evidence for nicotine's role in pathological mechanisms in schizophrenia that may allow a new line of investigation to be set up to analyse what causes this distressing illness and how it can be treated. This after all is the Rosetta Stone of research in the field of psychiatry.

SECTION 7

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